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EVERY MAN'S LEGACY*

Presidential Address

ARTHUR B. HUNT, M.D., ROCHESTER, MINN.

(From the Section of Obstetrics and Gynecology, Mayo Clinic and Mayo Foundation†)

EACH one of us has a heritage from our early teachers of obstetrics and gynecology. Today I wish to talk of this heritage and to persuade each one of you to reflect on the men who helped to train you and left a permanent influence on you. Some of you will need to hark back several decades while others may need recall men who are still alive and active, many of whom probably are members of this Association.

Medical education now seems to be undergoing another period of self-examination and evaluation somewhat similar to that conducted by the Rockefeller Foundation through the efforts of Simon Flexner in 1910. Much is heard of permanent or temporary changes in the undergraduate curriculum, innovations in graduate teaching of the specialties, and even of plans for the rapid training of general practitioners in the various specialties. In reports and discussions of these new departures in medical teaching, emphasis is placed—and probably properly so—on the teaching of facts and principles of pathologic physiology and therapy. Virtually no mention is made of the personal side of pedagogy, yet that is the aspect of the medical educative process which I wish to consider.

*Presented at the Twenty-fifth Annual meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of University of Minnesota.

In one of the papers just mentioned which deals with educational changes, the statement was made that the educational experience must necessarily be an emotional one. To have an emotional experience without interplay of personalities is rather difficult. It may be possible to instruct medical students and graduate students in our specialty by a variety of canned techniques with such mechanical devices as tape recorders, amplifiers, and loud speakers. It may be possible to "instruct" them in facts and some principles and even a modicum of what we call "judgment" by well-chosen aphorisms presented by automation, but I doubt if the process can be depended on really to "educate" the obstetricians and gynecologists of the future. Knowledge is only a part of the educative process and George Bernard Shaw's black girl in her search for God* had this well in mind when she inquired, "How much better will the world be when it is all knowledge and no mercy?"

If we accept, then, the necessity of the individual teacher and preceptor, who are they? In early life they are obviously our parents who give us confidence in their wisdom and other older relatives and friends who care for us and are interested in us. These include our elementary and secondary school teachers, our religious teachers, and the exemplary banker, lawyer, or physician of the community. I dare say many of you here were motivated to study medicine by the example of one or more older physicians who either showed interest in you or perhaps unconsciously by splendid example influenced you to desire to become a doctor. Many of you, too, had college teachers in the premedical period whose memory you hold with gratitude and affection for inspiration and help.

I am one of that minority who feels that four years in a small liberal arts college is not an educational luxury, in spite of the long weary course through medical school, internship, residency, and that period of practice required before a man becomes finally Board certified as a specialist in the field of obstetrics and gynecology. These four years of a liberal arts course can give a little sounder and less hurried grounding in the basic premedical sciences, but, of more importance, they furnish a cultural background for the remainder of the student's life. Some time spent in the study of philosophy, religion, biography, literature, and history will orient the future physician and give him a cultural sense of poise and relative values that nothing else can supply. A smattering of economics and public speaking too may be available, which are not offered in the medical schools as a rule. Finally, in the smaller colleges, at least, the faculty members are interested in individual students or they would not so often remain there dedicated to those colleges in spite of opportunities for so-called advancement. Personal contact with such teachers may be the finest inspiration for character development in these formative, more idealistic years.

I have already implied that in most cases our first inspiration to go into medicine was often the example of some fine physician whom we admired as

*Shaw, George Bernard: The Adventures of the Black Girl in Her Search for God, New York, 1933, Dodd, Mead & Company.

boys. In my own case, that physician was my father. Since I did not have opportunity to observe him beyond my seventeenth year, I do not know first hand of his professional competency, but I have often been told by those who did know that it was of good order. I do know he had a quiet and abiding love for the practice of medicine in both its intellectual-scientific and human relations aspects. He was devoted to his patients, and they reciprocated this loyalty. As a small town general practitioner I know he enjoyed, and was proficient in, the conduct of a rather large obstetric practice. By word, and especially by deed, my brothers and I were taught that the stewardship of service to others is not only a duty but a coveted privilege productive of one of life's greatest satisfactions. My father further believed it a duty to perform some public service in the community and was long president of the school board and mayor of the town for two terms and held other, minor positions of trust. I remember him gratefully for pleasant good humor, courageous equanimity under stress, and for thoroughness, honesty, loyalty, self-respect, and constant friendliness—all qualities that can be an asset to any physician of the present day whether in a specialty or not.

From this point onward we must each go our own way, as of course I do not know the teachers that each of you had, although in some cases they may be the same ones I had. I know each of you could speak of them as well as I, but of my teachers of obststrics and gynecology I shall speak now.

By good fortune Jennings C. Litzenberg was my professor of obstetrics and gynecology at the University of Minnesota. A dynamic and forceful teacher of clinical obstetrics and gynecology, he held this chair at his alma mater and served with great effect and distinction from 1913 until 1938. Of prerevolutionary American parentage, Dr. Litzenberg was born in Iowa and came from high school to Minnesota in 1890 with his widowed mother so that he could attend the University of Minnesota. During his junior year his eyesight failed and he entered the senior year of premedical work with the demoralizing prospect of nine "incompletes" and one "condition." After his vision was corrected he stated, "With 100 per cent vision I had courage to tackle the discouraging situation of the senior year. I was happy to graduate with one extra credit."

For Dr. Litzenberg to secure a medical education was a struggle. In his undergraduate days he worked in a grocery store. With insufficient funds to enter the Medical School of the University of Minnesota he dropped out of school and served as Superintendent of Schools at St. Louis Park, now a large and flourishing suburb of Minneapolis, for one year. While in medical school he was successively Educational Director of the Minneapolis Y.M.C.A. Evening Schools, Acting Secretary-General of the same organization, and Assistant Physical Director of the University of Minnesota gymnasium.

Years later, students, associates, and friends all knew Dr. Litzenberg affectionately as "Litz." While usually in good control of his temper, on occasions he felt justified in striking fear among students through incisive and well-directed, but never unfair, asperity. Teaching at a time when there

was no effective treatment for the dreaded and often fatal puerperal sepsis, he was keenly conscious of the high rate of maternal mortality from all causes and he stated simply, in an autobiographical sketch, "I gave my teaching life to this problem." His vigorous, sound, and conservative teaching of undergraduates, interns, and residents has been generally credited as a major contribution to the consistently low maternal mortality rates of Minnesota and adjacent states. He followed the progress of his students and took delight in their successes whether such successes were achieved by performing good obstetrics in general practice in a small Minnesota or Dakota town or by creditably occupying the chair of obstetrics and gynecology in an important university.

Litz had a boyish but sophisticated enthusiasm for all facets of life and was an optimistic but realistic man. He had a chuckling type of humor and enjoyed a joke fully even though it was on him.

A versatile man, he was able to carry along successfully and simultaneously nearly a dozen phases of medical activity such as his private practice, his professorship at the university with its teaching, investigative work and administrative responsibilities, a large consultation practice, demands made on him as a medical speaker, and a decade of service as an original member of the American Board of Obstetrics and Gynecology.* During these years he voluntarily spent much time with his secretary in detailed correspondence trying to get the best possible internship for each of the hundred or so graduating seniors each year. Many a Minnesota medical graduate looks back with gratitude for this help he received from Litz.

Because of the solid quality of his practice and his contributions to the literature of his specialty together with his forcefulness as a speaker and his affable charming personality, he was the first, in recent decades at least, to be elected President of both the American Gynecological Society and the American Association of Obstetricians and Gynecologists, as well as Chairman of the Section on Obstetrics and Gynecology of the A.M.A. He was also President of this Association in 1940. In spite of these national honors, he maintained an active loyalty and made contributions to his community and state. He was early president of his county society, the Minnesota Academy of Medicine, and the Minnesota Obstetrical and Gynecological Society, and said that he prized these honors by his home societies because the members knew his faults.

The next teachers I encountered were at the Indiana University Hospitals in Indianapolis during my internship. There I came under the tutelage of Dr. A. M. Mendenhall who was relatively young and energetic and ran a well-organized department. He was a master at bedside and dry clinic teaching and had a ready reference to the current literature. His progress to prominence in American obstetrics and gynecology was cut short by an untimely death in an airplane accident. C. O. McCormick, Sr., also taught effectively there, both formally and by example.

*Drs. Adair, Mussey, and Plass gave similar service to the "original" Board.

My three-year residency in the Chicago Lying-in Hospital was preceded by a six-month internship "on the district" as it was called in the old Chicago Lying-in Dispensary, now the Chicago Maternity Center. The depression had fully developed, but the resources for relief had not yet been organized. The case load mounted monthly but the personnel did not. There was a wealth of obstetric material and one learned to be alert for complications and deal with them with a minimum of physical equipment under conditions of dirt and misery. Dr. George E. Hudson, now of Minneapolis, was the consultant on this service and taught ultraconservative but sound obstetric fundamentals with equal interest and trenchant English day or night as complications arose frequently.

During my residency in Chicago I had the great privilege of serving under and learning from two of the country's outstanding men in our specialty, Drs. Joseph B. DeLee and Fred L. Adair. As an undergraduate I had attended lectures by Dr. Adair and served a clerkship in obstetrics under him at the Minneapolis General Hospital before he went to Chicago.

Strangely enough, both he and Dr. Litzenberg had come to Minnesota from the small Iowa town of Anamosa which now numbers 4,000 people and has recently been chosen as a typical small midwestern town for television showing in Europe under direction of the United States Information Agency.

Dr. Adair was a methodical and prodigious worker who practiced and taught careful attention to detail and accuracy. He apparently believed in the adage that "trifles make perfection but perfection is no trifle." He was cool and effective when confronted with major obstetric and gynecologic surgical crises. He was a gifted organizer and administrator and was responsible for interesting the government through the Children's Bureau in the prenatal care movement and in reduction of maternal mortality. If any one individual could be called the "father of modern prenatal care," it is Fred L. Adair. He is one of the three living founders of the Central Association of Obstetricians and Gynecologists.

In 1930 Joseph B. DeLee shared the deanship of American Obstetricians with Dr. J. Whitridge Williams of Johns Hopkins University. Their complete and authoritative textbooks which have been ably carried on by their successors are only one evidence of this eminence. A colorful and brilliant practitioner of medicine with a tremendous clinical experience, DeLee's one interest in life was obstetrics. He glorified motherhood in an idealistic and even spiritual way which was sincere. Relieved and deprived, as a bachelor, of the cares and rewards of parenthood, he gave almost his entire life, a career of about 50 years, to the perfection of the art and science of obstetrics, with emphasis in his later years on teaching. In spite of this, his knowledge of the arts, humanities, and comparative religion was often surprising. He was a perfectionist and solicited those associated with him to join him in the quest for perfection. He could criticize frankly and sharply but was constructive and never hurtful. He thought of himself as progressive and made innovations,

some of which failed to have merit, but several of which have endured and are now common practice. He was labeled "radical" by some. He was not averse to a bit of dramatic showmanship to advance some phase of obstetrics.

Dr. DeLee was warmhearted when he observed difficulty or misfortune and was always gracious and helpful in consultation with a colleague with a major obstetric problem. Any patient who was seriously ill in his hospital was eligible to receive the benefit of his professional talent and did receive his worried concern. Indigents sometimes were provided with special nursing care from his pocket. He had few social intimates and probably went through periods of lonely and even melancholy introspection. One of the interesting teaching activities he carried on for a time during my residence was a late Wednesday afternoon seminar to which he brought inquiries from physicians in this country and elsewhere on rare obstetric problems and complications. He would call for suggestions and then from his experience explain the how and why of the answers he proposed to send.

Dr. DeLee personally founded with modest beginnings a maternity hospital that he developed till it achieved an international reputation. He was in the vanguard with several others of his era in establishing obstetrics as a recognized, important, and special branch of medicine.

During my residency the junior staff of the Chicago Lying-in Hospital was formed at the time of the move to the University of Chicago and it consisted of Drs. W. J. Dieckmann, M. E. Davis, and H. C. Hesseltine. Dr. Dieckmann, or "Dieck," as he was known to us, was a scientific scholar of high quality. In his knowledge of the physiologic and chemical background of the toxemias of pregnancy he was probably never surpassed by anyone to the time of his death this year. Much of this knowledge resulted from his own careful and persistent research. He was a generous teacher of operative techniques in both obstetrics and gynecology. Dr. "Maurie" Davis was already a skillful technician and clinician in the specialty and has since carried out much creditable research, especially in the field of endocrine gynecology. Dr. Hesseltine's long-standing studies on vaginitis are well known.

The courtesy staff of the Chicago Lying-in Hospital at that time was also liberal with teaching efforts. Dr. David A. Horner, a master of the use of the obstetric forceps, voluntarily spent many hours with the interns and residents discussing their use with supplementary demonstrations on the manikin. Drs. J. P. Greenhill, E. L. Cornell, and many others of this group are gratefully remembered.

During 1934, while in practice in Cedar Rapids, Iowa, I was able, through the hospitality of Dr. E. D. Plass, to attend the weekly staff meetings of his department at the University of Iowa. Dr. Plass and his department were productive in both clinical and fundamental investigation and these sessions were provocative and stimulating. Drs. William F. Mengert and John H. Randall were key staff members in that year. Dr. Plass was an intellectual iconoclast in the best sense of the term and often debunked some venerated procedure of really unproved value to simplify patient care.

In Cedar Rapids at that time was Dr. William Brown, a self-made obstetrician of the old school who did a fine job of helping out his general practitioner colleagues in the area when they were in obstetric difficulties. He was a devoted charter member of this Association who seldom missed a meeting and once served on its executive committee. His loyalty, dry humor, simple honesty, and unconcern for financial gain are recalled with affection.

At the Mayo Clinic the department in which I serve was headed by Dr. Robert D. Mussey and lately by Dr. Lawrence M. Randall. Dr. Mussey was originally trained in internal medicine, and this may explain why his major investigative subjects were such conditions as the toxemias and thyroid disease in relation to obstetrics. After further training in obstetrics, he founded the obstetric service at the Mayo Clinic and at St. Mary's Hospital in 1922. Dr. Mussey was a true gentleman, looking and acting whenever possible on the good side of a situation. Friendly and quietly gregarious, he was cheerfully helpful to his contemporaries and maintained an almost fatherly interest toward younger staff men and the fellows in his and other departments. His colleagues can attest to his diagnostic skill in both obstetrics and medical gynecology, and his patients in great numbers have not forgotten his courteous and sympathetic handling of their interests. He served the clinic in which he worked with staunch loyalty and ability in a top administrative post for over a decade in the trying years before, during, and after World War II.

Another highly respected administrator at the Mayo Clinic for more than 40 years once said of Larry Randall that he has the unique ability of being both popular and a good administrator. His facile mind, when faced with a major obstetric or gynecologic problem, can come to proper diagnostic and therapeutic decisions by adroit observation and discerning judgment promptly and with very little ado. His sly sense of humor has often been a delight. He has been singularly able at the informal type of teaching which is so often used at the graduate level. I could say a good deal more but it would be poor etiquette as he is still technically my boss and he is here today and it would bother him!

Of course it is understood that an obstetrician and gynecologist can never hope to be well informed without reading faithfully the correct journals, but you recall that I am talking about the personal side of teaching.

Obviously, too, we learn much from our contemporary professional friends by formal and informal association at meetings such as this and when we sit down in small groups with one another. This can be the most pleasant, stimulating, and successful kind of teaching and learning. We learn from our juniors in daily work and from our residents. They keep us young and hold our interest in our life's chosen field, but I have necessarily confined myself today in the main to the learning of the younger years through older teachers.

I have not given these thumbnail sketches of my teachers to point out boastfully their number or quality, although I do think I was extremely fortunate. I have done so with the hope that each of you will contemplate

the legacy of preceptorship that has been yours so that you may rededicate yourselves to our specialty. Some of you may think that you do little or no teaching, but I believe each of us does teach in some capacity and to some extent. The finest teacher motivates, inspires, and affects the development of intellectual acuity, honesty, accuracy, and critical judgment in the student. The student to be worthy of this legacy should feel an obligation to perpetuate it later through his own students. We have the duty and the opportunity to see that our teachers have not taught in vain. If we dwell for a time on the examples set by our teachers, we may transmit some of the good that was theirs to the younger men we teach. If we can thus transmit some of the pedagogical virtues from the past generation through us to the future, we may establish for our teachers some of the true immortality that by right should belong to the fine teacher. The oft-quoted line from Henry Adams perhaps expresses it best, "A teacher affects eternity; he can never tell where his influence stops."

CURRENT TREATMENT OF CARCINOMA OF THE CERVIX*

H. L. KOTTMEIER, M.D., STOCKHOLM, SWEDEN

(From the Radiumhemmet)

CONTROVERSY on the management of cervical carcinoma still continues between the advocates of surgery and of irradiation. Excellent results by radical hysterectomy in selected cases of cervical carcinoma have been reported by Meigs, Brunschwig, Navratil, and others. Although the primary mortality is low, the price we have to pay for the surgical procedure is still high. Fistulas are the most annoying complication and occur in about 10 per cent of nonradiated cases. The permanent results achieved by primary adequate radiotherapy in an unselected series of cases of carcinoma of the cervix seem to me to be superior to those by surgery. Irradiation should, therefore, be the primary treatment in all cases of invasive carcinoma. Serious injuries from radiation, such as fistulas, ulcers, or stenosis, occur only rarely in cases of operable cervical cancer. The frequency of such complications is of course increased in the irradiation of the more advanced tumors, but at the Radiumhemmet severe injuries have occurred in 1.1 per cent of the cases.

The Annual Reports

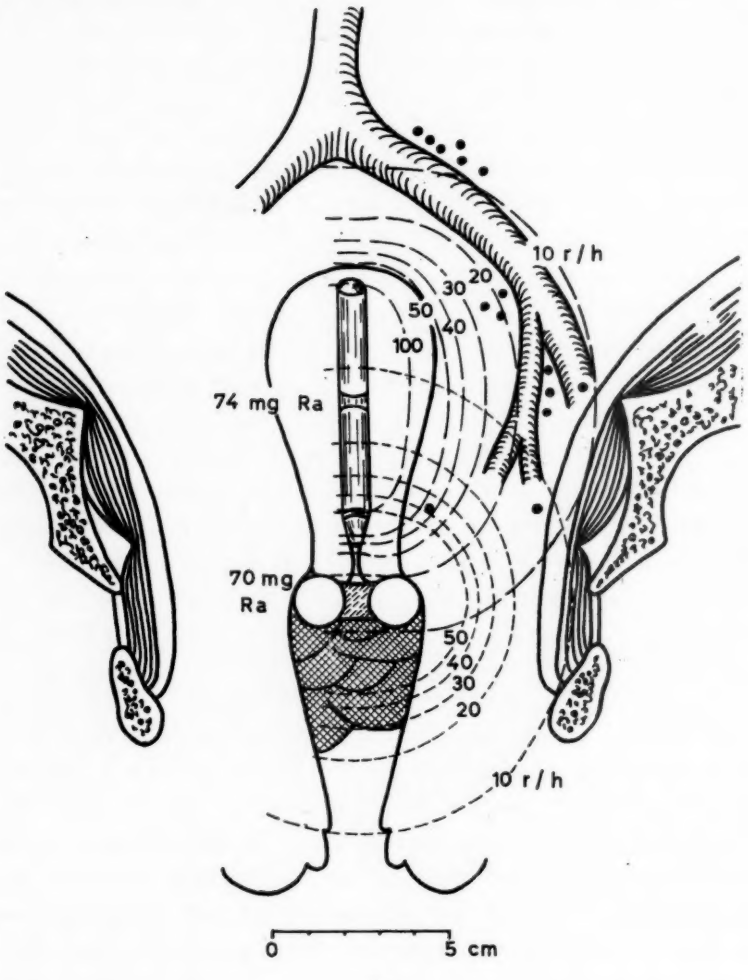
It is true that a comparison of therapeutic results obtained at different institutions is difficult. Such a comparison is the purpose of the *Annual Report on the Results of Treatment in Carcinoma of the Uterus.* The last, and still unpublished, report includes statements from 78 institutions and furnishes information concerning 98,218 treated cases. A study of the results on material from the last 5 years shows an over-all relative apparent recovery rate of 41.5 per cent. The recovery rates are: for Stage I, 67.0 per cent; Stage II, 47.8 per cent; Stage III, 27.2 per cent; and Stage IV, 7.1 per cent.

Many gynecological societies and cancer societies have emphasied that the *Annual Report* is of paramount importance. The International Federation of Gynecology and Obstetrics will accept the sponsorship of the report. We hope that this will stimulate many institutions to collaborate and thereby improve our facilities for studying the results achieved by various techniques.

Experience has shown the importance of further subdivision of the International Classification. For instance, an early Stage I carcinoma is quite a

*Address of the Guest Speaker, presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

different disease from a Stage I cancer destroying the whole cervix. A questionably invasive carcinoma in situ will be allotted to Stage 0 at one institution and to Stage I at another clinic. These are facts that will considerably influence the results. This holds true also for Stage IV, where some clinicians require a positive biopsy while others accept bullous edema as evidence of bladder invasion.



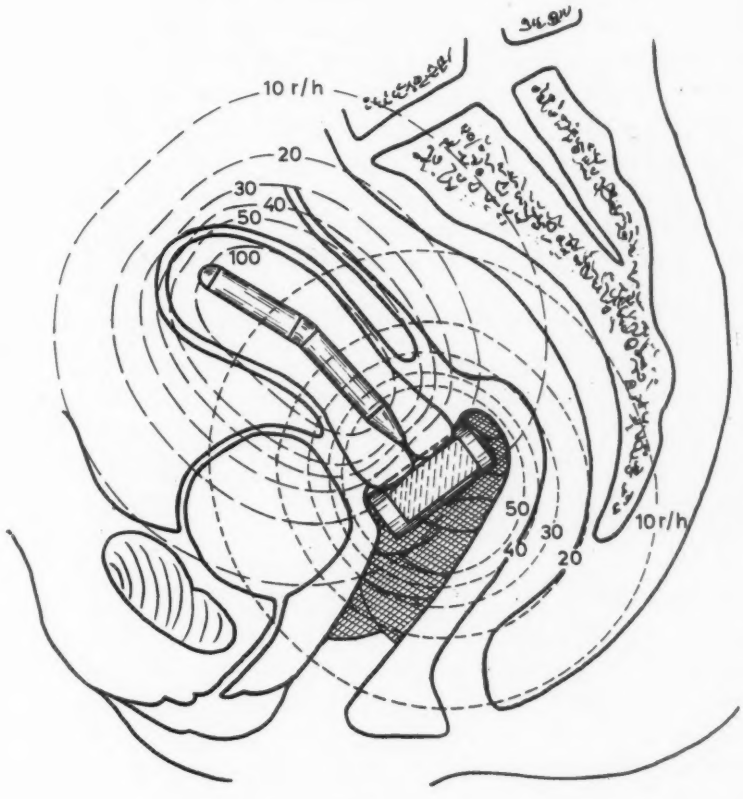
A.

Fig. 1, *A* and *B*.—Isodose curves from intrauterine and vaginal radium applicator. Standard technique.

Significance of Primary Healing

In many cases primary healing will occur within 6 months, but sometimes it takes more than 6 months or even one year. It is true that the number of failures is increased in cases of late primary healing, but it is also true that the finding of malignant cells in smears or biopsies within 6 months following completion of adequate irradiation does not permit any conclusion as far as radiocurability is concerned. Primary healing was obtained in 96.1 per cent

of 372 cases allotted to Stage I, treated at the Radiumhemmet from 1936 to 1947. The corresponding rate in Stage IIA was 90.2 per cent; Stage IIB, 77.1 per cent; Stage III, 56.5 per cent; and Stage IV, 37.3 per cent. A recurrence may appear in the uterus, the vagina, the paracervical or paravaginal tissue, the pelvic lymph nodes, or in other parts of the body. The vast majority of recurrences occur during the first years. Recurrences in the cervix or vagina have occurred in 8.3 per cent of the cases allotted to Stage I in which primary healing was obtained; 10.7 per cent of Stage IIA cases; 11.4 per cent of Stage IIB cases, and 8.8 per cent of those allotted to Stage III. Routine Papanicolaou smears can be a valuable adjunct in detecting recurrent tumors.



B.

Management of Recurrent Cases

The management of persistent or recurrent cancer is evidently dependent on the site of the growth. In cases of suburethral metastases or tumor in the vaginal wall, reirradiation by the use of radium toward the mass and the surrounding tissues (2,800 gamma r at 2 cm. depth), intravaginal cone, teleradium, or x-ray therapy is of considerable value.

Survival for 5 years or more after the treatment was applied has occurred in 22 per cent of such cases. From our experience, however, reirradiation is

of little value in treating persistent or recurrent carcinoma in the cervix or upper vagina, provided the case was treated adequately the first time. We do feel that there is a definite place for radical hysterectomy, pelvic exenteration, or extensive electroendothermy in the treatment of these cases.

Nordenstrahl has studied 2,174 patients primarily treated by radiotherapy at the Radiumhemmet from 1945 through June, 1951. Surgery for persistent or recurrent carcinoma has been carried out later in 180 cases, i.e., in 8.3 per cent. Radical hysterectomy was the procedure in 50 cases, a Schauta operation in 3, and an exenteration in 3. Thirteen of these 56 patients are living, symptom free, 5 years or more after the operation, i.e., a recovery rate of 23.2 per cent. Urinary fistulas occurred in 6 cases. In one of the 13 patients who survived 5 years, the cancer had extended to the parametrial tissue.

In 124 cases, an extensive electroendothermy with a strong monopolar current from the long-wave diathermy was carried out. The fulguration has a definite place in the treatment of radio-incurable carcinoma. A deep coagulation out to the pelvic wall was done in 35 of the 124 cases mentioned. Six patients are living without any evidence of disease at 5 years, i.e., a recovery rate of 17.1 per cent. The survival rate was 30.6 per cent in all 124 cases in which a fulguration was carried out. Two patients died following the procedure, one from hemorrhage, one from peritonitis.

Radiosensitivity and Radioresistance

Obviously it is true that some cases of cervical carcinoma are radio-incurable. We do not know whether we may cure them by surgery. It would be of value, however, if we could foretell which cases have a poor chance of being radio-incurable. In our experience, there is no correlation between the radiocurability of the growth and the maturity of the cancer cells, nor is the radiocurability in adenocarcinoma of the cervix worse than in epidermoid carcinoma.

The thorough study by the Grahams on sensitivity response in vaginal smears has shown that there is a fair chance of predicting the clinical course of a cervical carcinoma. Serial biopsies taken during the course of treatment are also of value in predicting the radiocurability. Personally, I would prefer the cytologic method, especially as it is nontraumatic. We have noted a 4 year cure rate of 64 per cent and 41 per cent in good and poor SR, respectively, in 99 cases treated in collaboration with Drs. Ruth and John Graham.

Techniques of Radiation

In our experience, the first step of irradiation should be the intracavitary application of radium, provided the radium can be satisfactorily applied and the external os is easily located. Roentgen therapy as the first step of irradiation is given only in far-advanced carcinoma and in large cauliflower tumors. In cases of advanced carcinoma we give roentgen therapy with 200 kv. through one large anterior and two posterior portals, administering a dose of about 3,000 r in 3 to 3½ weeks to the posterior fornix, prior to the application of radium. In cases of large cauliflower tumors, x-ray is given through two perineal portals; 6 times 400 r to each portal.

The intrauterine and the intravaginal radium application we like to carry out so that the best possible dosage distribution will be given to the area where we feel cancer may extend. This requires a careful pelvic examination by a skilled gynecologist, especially with regard to the extension of the growth, urography, and sometimes venography. Venography is of significance in order to localize the area of suspicious pelvic node metastases.

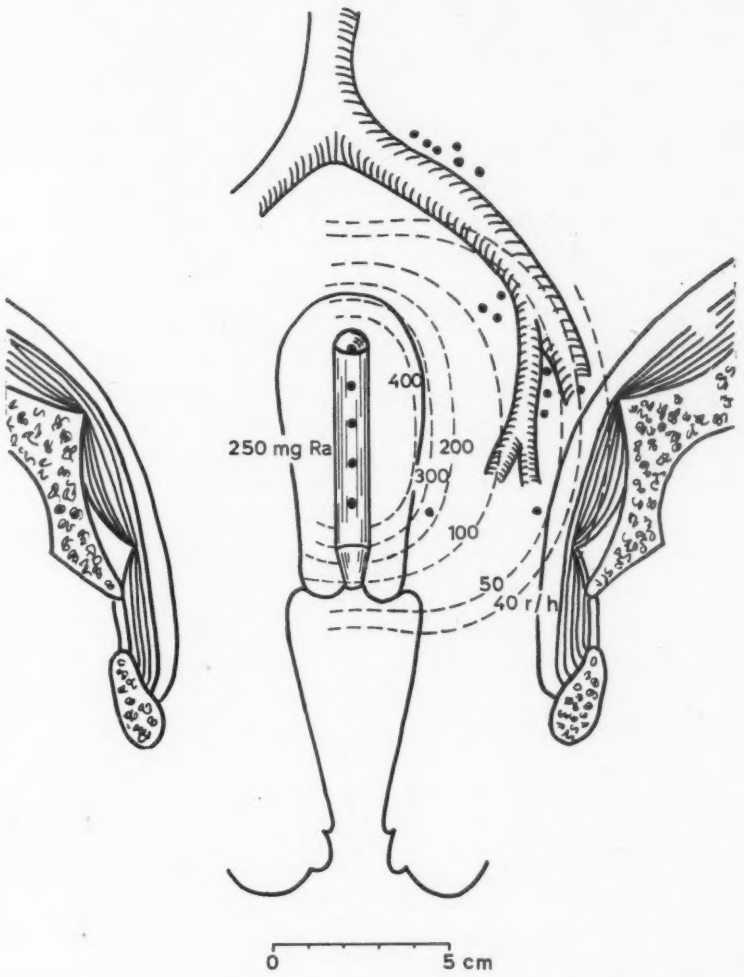


Fig. 2.—Isodose curve from intrauterine applicator with increased intensity.

Individualization of the intracavitary radium treatment requires understanding of the fundamentals of radiation and physics. The isodose curves for the different intravaginal and intrauterine applications should be worked out and be available at the time of the individual application. For instance, the radium application in a patient with a narrow vagina should be quite different from the application in one with a large vagina. The intrauterine radium is to a much greater extent responsible for the dosage in the paracervical tissue and in the pelvic nodes than the vaginal radium, and the contrary is true as far as the paravaginal spread of the cancer is concerned. This applies, for instance, to cases of endocervical carcinoma or those with a

Fig. 3.

Fig. 4.

Figs. 3 and 4.—Venograms in patients with carcinoma of the cervix. Note anatomical variation.

paracervical spread of the neoplasm. The dosage from the intrauterine radium should be considerably increased in such cases and the vaginal dosage decreased. Thus, in a case of endocervical carcinoma, Stage I, the application of radium should be quite different from that in a disc-shaped carcinoma in the portio (Fig. 1, *a* and *b*).

As a rule, the dose delivered is given in milligram hours, or in gamma r to points A and B. We prefer to individualize the therapy and not to standardize it. The treatment time is determined in the individual case by a direct reading of the dosage in the posterior wall of the bladder and the anterior wall of the rectum. A small ionization chamber contained in a curved probe is inserted first in the bladder and then in the rectum to a depth of 14 cm. With the probe in the midline and with gentle pressure on the

Fig. 5.—Venogram in a case of carcinoma of the cervix, Stage II. There is compression of the external iliac vein due to metastasis.

wall, it is slowly withdrawn, and the dosage rate at each centimeter of distance is recorded. With the high intensity used in Stockholm the optimal dose in the bladder is about 5,500 gamma r and in the rectum, 4,000 gamma r, provided attention is given to the dosage in an area of 3 cm. or more. A higher dose will increase the risk of proctitis or bladder damage. Overradiation of normal tissue should be avoided. In our experience, fractionated irradiation is preferable. In uncomplicated cases, the intracavitary application is divided into two treatments with an interval of 3 weeks. In infected cases it is expedient not to apply the intrauterine and vaginal radium simultaneously.

Some years ago we were forced to try to limit the intracavitary radium treatment to one application in some suitable cases. The results were poor, probably because of localized injury to the resistance of normal tissue. A fractionated treatment is also valuable in that it is often impossible to decide on initial examination whether curative or palliative treatment should be the choice in a special case (Fig. 2).

In cases of endocervical carcinoma, of spread of the cancer to the paracervical tissue, and of pelvic lymph node metastases, an increase in the intrauterine dose is desirable. This can be realized by an increase in the time the radium is left in place or by an increase in the amount of radioactive material applied. We have tried both methods and have chosen an increased intensity. One hundred to two hundred milligrams of radium element is inserted into the uterine cavity, dependent on the length of the sound. The diameter of the applicator is increased in order to avoid necrosis in the uterine wall. The correct application is controlled by the probe inserted into the rectum. It is preferable not to exceed a dosage of 2,500 gamma r in 24 hours to the anterior wall of the rectum, and furthermore not to give external radiotherapy immediately after such an application.

Additional roentgen therapy is given to the pelvic wall from two anterior and two posterior portals in every case. Two thousand to 2,400 r is given to the pelvic wall in 24 to 32 days. Sometimes it is desirable to increase the dose to the pelvic wall. Continuous massive doses to a large volume of tissue should be avoided as this will increase the risk of irreversible damage. We give additional therapy to the area on the pelvic wall by telecobalt, using multiple, small, partly overlapping anterior and posterior portals. We avail ourselves of the divergency of the beam from a small cobalt source.

Prior to this additional therapy, however, we require a urovenogram for the purpose of obtaining information on pelvic anatomy. Sometimes an alteration in the venous system gives information regarding the spread of the cancer. Venography is desirable also prior to parametrial injection of radioactive colloidal gold, a method which has had a satisfactory palliative effect in many cases of recurrence in the pelvic wall (Figs. 3, 4, and 5).

TABLE I. FIVE-YEAR APPARENT RECOVERY RATES FOR THE YEARS 1938-1945, 1946-1948, AND 1949-1951 IN CASES TREATED AT THE RADIUMHEMMET

	1936-1945		1946-1948		1949-1951	
STAGE	NO. OF CASES	5 YEAR CURE RATE (%)	NO. OF CASES	5 YEAR CURE RATE (%)	NO. OF CASES	5 YEAR CURE RATE (%)
I	299	69.2	155	74.8	155	89.0
IIA	537	63.3	228	58.3	295	64.4
IIB	903	44.3	235	37.0	310	45.2
III	787	24.4	254	26.0	230	33.5
IV	230	11.3	78	2.5	91	7.8
I-IV	2,756	42.3	950	42.5	1,081	51.1
No treatment	119		34		11	

Results at the Radiumhemmet

The current individualized technique was started in 1949 at the Radiumhemmet. The marked improvement in the results supports the importance of individualization (Table I). One thousand and eighty-one patients were treated during the 3 years, 1949-1951. Treatment was refused in 11 cases. The oldest patient was 96 years of age, with a Stage I carcinoma. Fifty-three patients were 30 years of age or younger. Palliative radiotherapy, i.e.,

one radium treatment or a few x-ray treatments, was given in 7.4 per cent of the cases. Radical hysterectomy was carried out later in 43 cases of persistent or recurrent carcinoma, and fulguration in 83 cases.

The 5 year apparent recovery rate is 89.0 per cent in Stage I; 64.4 per cent in Stage IIA; 45.2 per cent in Stage IIB; 33.5 per cent in Stage III; and 7.8 per cent in Stage IV. Since 1949, a case is allotted to Stage IV only if invasion of the bladder or rectum is proved histologically, or distant metastases are present.

THE EVOLUTION OF A RESEARCH PROGRAM*†

ARTHUR T. HERTIG, M.D., BOSTON, MASS.

(From the Departments of Pathology, Obstetrics and Gynecology, Harvard Medical School, Boston, the Pathology Laboratories of the Boston Lying-in Hospital, Boston, and the Free Hospital for Women, Brookline, Massachusetts, and the Carnegie Institution of Washington, Department of Embryology, Baltimore, Maryland)

WHEN Dr. Arthur Hunt, your President, asked me to be a guest speaker before the Central Association of Obstetricians and Gynecologists, I was at a loss for a subject, the results of original researches having already been published or committed for publication. Occasionally I have spoken informally to the students of the Nu Sigma Nu Medical Fraternity at Harvard on how pure chance appears to influence significantly the course of a medical career. My own appears to have been so influenced. I propose to use this general point of view in sketching the evolution of the research program with which I have been associated during the past 25 years.

In 1921, when a senior in high school, I obtained a part-time job as an assistant in the Department of Entomology at the University of Minnesota. My brother, Marshall, working for his Ph.D. under Dr. William A. Riley, was instrumental in obtaining this job for me. My duties were to collect and mount insects for use by the zoology students, the class being taught by my brother. For the first time, I had an insight into the principles and practice of the scientific method. I shall always be grateful to Dr. Riley and the other scientists of that department for the opportunity to learn firsthand what science really is. Dr. Riley's dictum, "If you don't know something, the next best thing is to know where you can look it up," seems to have epitomized the point of view which pervaded the department.

An amusing though painful incident occurred during the summer of 1922 while I was collecting the pupae of the white-marked tussock moth, *Hemerocampa leucostigma* of the family Lymantriidae (Liparidae). After two days of collecting, I developed an intense urticaria which Dr. Harry H. Knight deduced was probably due to the hairs shed by the larva as it underwent pupation and which were mixed in with the silk of the cocoon. Although it was known that the hairs of certain caterpillars were irritating, it had not been realized that this particular one possessed urticating properties. At that time Paul M. Gilmer was a graduate student in the department. He became interested in my itch and the reasons therefor. The detailed working out of the anatomy of these poison setae or hairs was published in 1923.[1] He went on to do his thesis on the comparative aspects of the poison apparatus of other moth larvae which

*The work here summarized has been partially supported by the Milton Fund, Harvard University, the Carnegie Institution of Washington, and the National Institutes of Health of the United States Public Health Service (Grants C-2451, C-2034, C-2378, and C-1471).

†Address of the Guest Speaker, presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

resulted in the publication of his classic paper in 1925.[2] Chance certainly played a large part in Gilmer's choice of a thesis and it taught me a great deal about how observation, deduction, and experiment form the tripod upon which science rests.

Although I was fascinated by entomology, medicine seemed to have a stronger pull, probably because of my firm friendship with and admiration for the late Dr. William G. King, our family physician and one of the early graduates of the Peter Bent Brigham Hospital in Boston. While I was a freshman in medical school at the University of Minnesota, Dr. Riley arranged for me to go to China as an entomologic assistant to the Kala Azar Field Studies unit headed by the internist, Dr. C. W. Young. My brother was the medical entomologist of this group. This study was under the auspices of The China Medical Board of the Rockefeller Foundation. Work on the insect transmission of kala-azar was carried on in Hsüchow-fu in Kiangsu province and later in Peking (then so-called) when the civil war made it impossible to work in the central Chinese villages where the disease was endemic. While working on this problem my brother and I were successful in artificially feeding various sandflies of the genus Phlebotomus belonging to the moth fly family, Psychodidae. By such feeding techniques, published in 1927,[3] we were able to infect them with the nonflagellated forms of *Leishmania donovani;* one of the early demonstrations that the ultimately proved vector could be experimentally linked with the causative organism of kala-azar. Our animal transmission experiments as well as others were negative or inconclusive. It remained for Smith and associates[4] in 1940 to recognize the significance of "blocked" sandflies.* By this is meant the exuberant growth of Leishmania in the pharynx, esophagus, and anterior end of the intestine after the Phlebotomus had fed on plant juices, such as from raisins, subsequent to being infected by feeding on kala-azar patients. Repeated attempts of these "blocked" sandflies to refeed resulted in large numbers of kala-azar organisms being regurgitated into the susceptible experimental animals (mice and hamsters). It is interesting and somewhat ironic that Young's group discovered the susceptibility of the hamster to kala-azar, that my brother first devised a method for rearing sandflies, and that we were able to infect them readily without their having had a natural blood meal. Chance, I suppose, played a part in our failure and in Smith's success in transmitting kala-azar because our method of keeping the infected sandflies alive worked superbly but did not enhance the growth of the Leishmania, whereas Smith's technique did both. As an interesting side light, the mechanism by which bubonic plague is transmitted by the rat flea is similar, namely, regurgitation from a proventriculus mechanically blocked by myriads of plague bacilli.[5]

Lest we lose sight of the fact that chance is aided and abetted by other factors, it would be well to quote what Pasteur thought about chance from an inaugural lecture at Lille in 1854 when he told his students, "In the field of observation chance only favors the mind which is prepared."

*"The senior author (R. O. A. S.) was closely connected with this aspect of the work since the inception of experiments to determine the role of the sandfly in the transmission of kala-azar and two of the assistants at present entrusted with the work of feeding sandflies have had many years' experience in the handling of these insects at the School of Tropical Medicine, Calcutta. A report from one of them, therefore, that certain flies were found making persistent efforts to obtain a blood meal after puncturing the skin of the animal and failing to succeed, was carefully investigated, as such an observation had never been made before. Reports to the effect that certain flies took an unusually long time to obtain a meal of blood were not uncommon previously, as well as the fact that certain flies took a relatively very small amount of blood; but such flies unfortunately were not singled out for special attention, and whether they were heavily infected individuals or merely feeble ones which were unable to collect a full blood meal easily for reasons other than that their passages were obstructed with masses of flagellates cannot now be ascertained." Indian J. M. Research 28: 581, 1940.

Whether chance favored Smith and did not favor us in China during 1925-1927, it did favor me in the circumstances under which I met Dr. David L. Edsall, then Dean of the Harvard Medical School (to which I transferred in 1928). Dean Edsall chanced to be visiting the Peking Union Medical College at that time. Among other events, we met socially, I supplied him with a set of pictures of a Chinese funeral in lieu of those he might have taken when his own camera broke down, and finally demonstrated our sandfly technique to him with the last living sandfly available in the laboratory. What I would have done had I finished medical school at Minnesota, I know not. Transferring to Harvard Medical School at the end of my second year, however, put me upon a path which led to general pathology through the late Dr. S. Burt Wolbach, to obstetric pathology and obstetrics through the late Dr. Frederick C. Irving, to gynecologic pathology through the late Dr. Frank A. Pemberton, and to embryology through the late Dr. George L. Streeter and Dr. George L. Corner. My debt to these men is great.

A Career in Pathology With Excursions to Other Fields

How I chanced to meet Dr. Wolbach in 1929, then Shattuck Professor of Pathological Anatomy, depended upon my brother Marshall's work with him in 1922 on the bacteroids (related to Rickettsiae) of the cockroach. It so happened that Dr. Wolbach wanted an entomologist to work on parasitic control of wood ticks on the islands of Naushon and Martha's Vineyard near Woods Hole during the summer of 1929. This came between my third and fourth years in medical school. It is not difficult to see how I happened to go into pathology, having been stimulated by Dr. Wolbach.

The first contact with the Boston Lying-in Hospital came in 1931, soon after Dr. Irving became the Richardson Professor of Obstetrics. The hospital had no laboratory of pathology and it was the desire of the new Professor to have one. My being assigned to that duty was pure chance, I having learned of the opening from Dr. Wolbach and applied for the job as Resident Pathologist. I had no particular interest at that time in obstetric pathology, but a paying position in 1931 early in the depression was less common than it is today. The laboratory consisted of two rooms and a connecting passage where the fourth year obstetric externs had previously lived.

During the academic year of 1931-1932 the many problems of obstetric pathology became apparent to me: puerperal sepsis, perinatal mortality, toxemia, and spontaneous abortion, to name only the more important. The problem of the pathogenesis of hydatidiform mole interested me. The process in some way seemed to be correlated with absence or early death of the fetus, disappearance of a functioning fetal circulation, and consequent hydropic swelling of the living but avascular chorionic villus of the blighted or pathologic ovum. When, by chance, in 1933, I failed to get a residency in general pathology, I applied for a National Research Council Fellowship in Embryology to work on molar blood vessels with Dr. Streeter at the Carnegie Institution of Washington, Department of Embryology in Baltimore. This was at Dr. Irving's suggestion; he wanted me to learn something of the pathologic embryology of spontaneous abortion.

Soon after arrival in Baltimore, Dr. Streeter made it clear that nothing was known about the formation of blood vessels in the normal primate placenta, let alone the fate of those in the hydropic human chorion. The academic year 1933-1934 gave me an opportunity to work out the morphologic details of the origin of the blood vessels and mesoblast in the normal primate chorion,[6] using the early human material already in the collection and the superb macaque material being accumulated and prepared by the incomparable team of Drs. Carl Hartman and Chester Heuser. Briefly, the angiogenesis

study showed that the vasoformative and supportive connective tissue of the chorion delaminated de novo from the trophoblast (Figs. 1 and 2). Later, this principle was seen to be applicable, in human material, to the origin of the amnion and mesenchymal wall of the primitive yolk sac.[7]

The stimulation from Streeter, Hartman, and Heuser was entirely responsible for my interest in the development of early human embryos. The opportunity to collect and study such specimens came later upon returning to Boston. By chance I became pathologist to the Free Hospital for Women in 1938. At this time Dr. John Rock was there and much interested in all aspects of the pathology and physiology of reproduction.

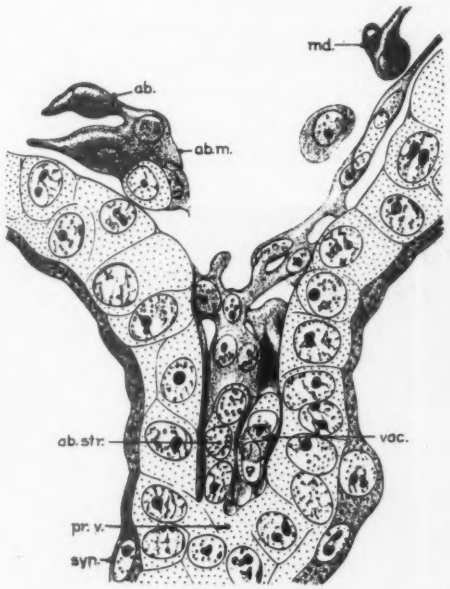


Fig. 1.

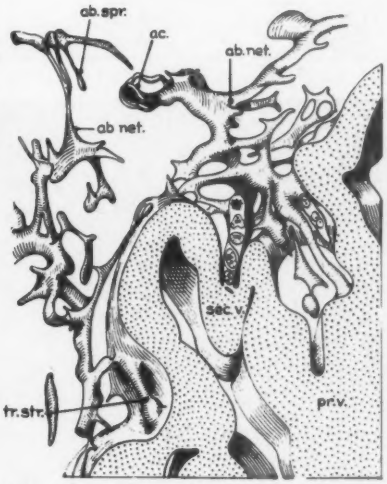


Fig. 2.

Figs. 1 and 2.—Angiogenesis in the primary placenta of *Macaca mulatta*. From Hertig.[6]
Fig. 1.—Reconstruction of 12 day primordial villus showing delamination of angioblastic masses and strands from cytotrophoblast of cell column at tip of villus. Carnegie No. C-467.
Fig. 2.—Reconstruction of vascular complex and chorionic villi from 17 day stage. Note relationship of vessels to cell columns of chorionic villi from which they were derived. Carnegie No. C-457.

My return to Boston and the Boston Lying-in Hospital as assistant pathologist enabled Dr. Henry Edmonds and me to survey systematically all the abortion material and to study those chorions which showed any degree of hyatidiform or hydropic swelling. From that study,[8] it appeared that this process is not one of a "degenerative" nature but a physiologic one whose basic principle rests upon the disappearance of a functioning fetal blood supply from chorionic villi whose trophoblast is still living. Hence, hydatidiform swelling is usually encountered: (1) at the margin of normally developing placentas, (2) in blighted or pathologic ova, and (3) in the occasional immature or mature placenta whose fetal chorionic vessels are deficient or fail to join up with the main chorionic circulation. This gross principle is illustrated and compared with the normal in Figs. 3 and 4.

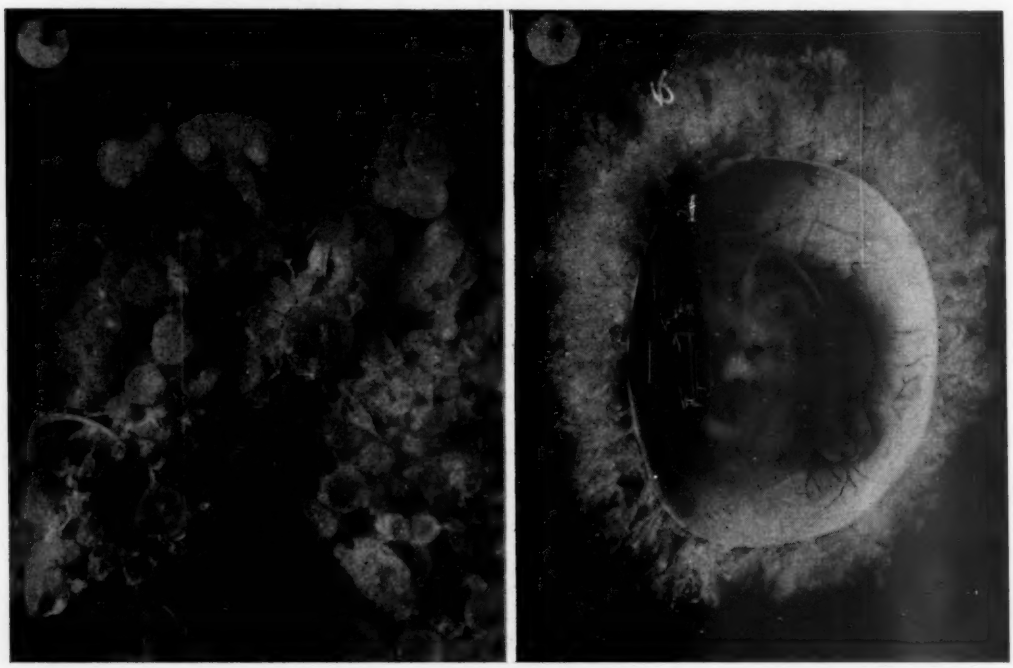
Fifteen years later came the chemical proof by McKay and co-workers[9] in our laboratory that fluid from hydatidiform molar villi and that from immature chorions are similar, each arising by activity of living trophoblast. His data are herewith summarized in Tables I and II.

TABLE I. COMPARISON OF FLUID FROM HYDATIDIFORM MOLES AND MATERNAL SERUM
(Data from McKay et al.[9], Paper I)

	MOLE FLUID	SERUM
Na^+	123	136
K^+	6.7	5.0
Cl^-	107	115
Protein	1.07	6.1
Osmoles	0.254	0.275

TABLE II. CHEMICAL CONSTITUENTS OF AMNIOTIC AND CHORIONIC FLUID FROM EARLY HUMAN PREGNANCIES TOGETHER WITH MATERNAL SERUM OF THE PATIENTS FROM WHOM THE SPECIMENS WERE OBTAINED
(Data from McKay et al.[9], Paper II)

	AMNIOTIC FLUID	CHORIONIC FLUID	SERUM
Na^+	120.	132	136
K^+	4.34	5.3	5.0
Cl^-	103.4	113.2	115
Protein	0.35	0.733	6.1



Figs. 3 and 4.—Hydatidiform mole and normal pregnancy for comparison of their gross characteristics. (About natural size; reduced 1/6.)

Fig. 3.—The macerated stunted embryo emphasizes the origin of the mole from a blighted or pathologic ovum, the chorionic villous branches of which undergo progressive swelling following cessation of the fetal circulation. Carnegie No. 8723, sequence 1. (From Meigs and Sturgis, editors: Progress in Gynecology, Grune & Stratton, vol. 2, chap. 7.)

Fig. 4.—A normal human pregnancy of approximately 9 weeks' menstrual age. Note frondlike chorionic villi, normal embryo, relatively small but normal amnion which fails to fill chorionic sac, normally functioning yolk sac, and well-vascularized chorion. Carnegie No. 8537-A. (From McKay et al.[9])

The accumulation of 200 hydatidiform moles from all over the country gave Dr. Walter Sheldon and me an opportunity to study the morphology of the trophoblast and correlate it objectively with what was found in the uterus and with the clinical outcome of the patient. Briefly, this study[10] showed that

although the morphology of the individual mole gave no precise prognosis for the patient, the degree of trophoblastic dedifferentiation was closely correlated with the tendency of the trophoblast to invade the uterus locally as a chorioadenoma destruens and/or metastasize as a chorioncarcinoma. That this principle still holds true has been shown by Dr. Brian Little* of the Boston Lying-in Hospital, working with 205 additional hydatidiform moles accumulated between 1943 and 1952. The original classification into six morphologic groups is cumbersome, moles being better graded simply as apparently benign (Grade 1), potentially malignant (Grade 2) and apparently malignant (Grade 3) as we now do in the laboratory.[11]

The intrinsic difficulty in predicting morphologically whether a given mole will give rise to choriocarcinoma—the real reason for scrutinizing a mole—is because of the invariable failure of a mole, giving rise to a choriocarcinoma, to show the morphologic pattern of its neoplastic sequela. This fundamental morphologic discrepancy is well illustrated in Figs. 6 and 7.

In 1938, following 19 months in clinical obstetrics under Dr. Irving, an opportunity came to become the pathologist at the Free Hospital for Women while still remaining in a similar capacity at the Boston Lying-in Hospital.

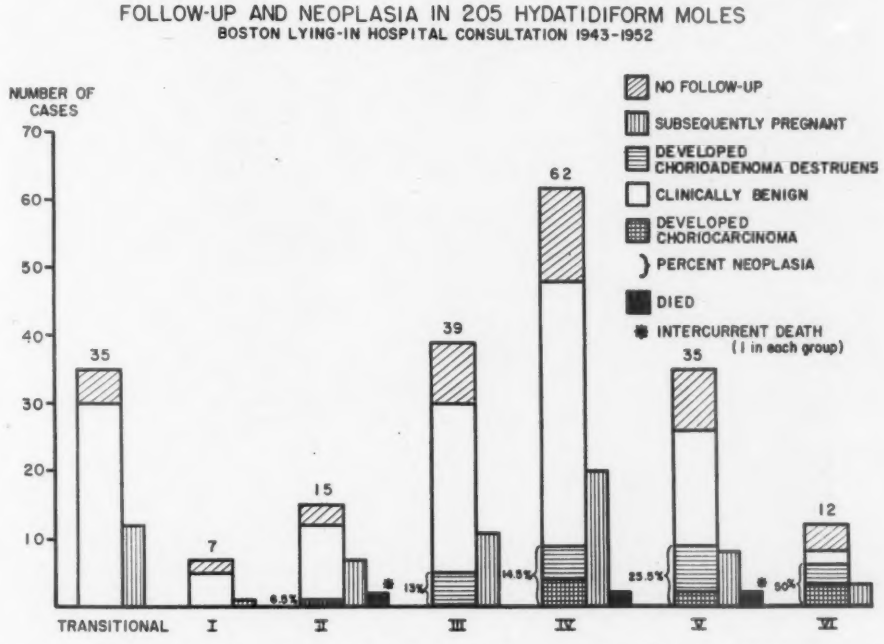
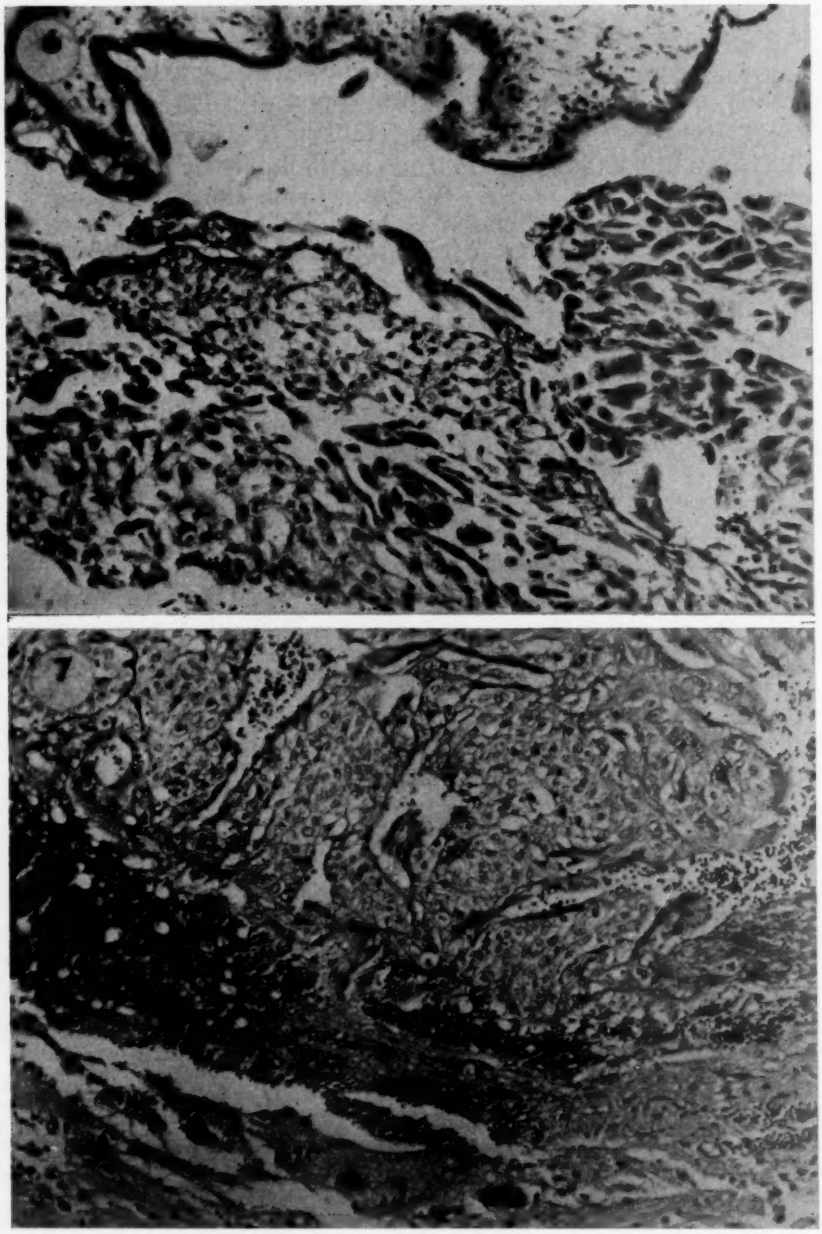


Fig. 5.—Follow-up data and subsequent neoplasia following 205 hydatidiform moles as grouped by Dr. Brian Little, using the Hertig and Sheldon's morphologic criteria. Note the relative increase in the incidence of chorioadenoma destruens and choriocarcinoma following moles whose trophoblast was less differentiated or potentially more malignant in appearance. (Courtesy of Dr. Brian Little, Boston Lying-in Hospital, unpublished data.)

Although Drs. John Rock, Gregory Pincus, and I had been searching Fallopian tubes for recently ovulated human ova, fertilized as well as unfertilized, since my return from Baltimore in 1934, we had found nothing. My coming to the Free Hospital gave Rock and me additional opportunity to select patients of known fertility coming to operation and to search in the removed uteri and tubes for early human conceptuses. This program has continued to the present

*Unpublished data.

time, but is now necessarily hampered by such factors as changes in hospital patient load (there is now no waiting list from the Clinic), Dr. Rock's retirement from the active staff, and my being at Harvard Medical School as a full-time teacher and administrator.



Figs. 6 and 7.—A malignant-appearing hydatidiform mole and the choriocarcinoma which resulted therefrom to illustrate the fundamental principle that no matter how malignant the molar trophoblast appears, it is not morphologically identical with its neoplastic derivative. From Hertig and Sheldon[10] and Hertig and Mansell.[11]

Fig. 6.—Note great pleomorphism of trophoblast and that, although it has both syncytio- and cytotrophoblast, it does not have the same pattern as is seen in Fig. 7. Leary Laboratory P-36-1370. (×110.)

Fig. 7.—Choriocarcinoma, metastatic to brain, following hydatidiform mole shown in Fig. 6. Leary Laboratory P-37-855. (×110.)

Although Rock and I had had some experience with the various normal and abnormal aspects of uterine and tubal morphology, both gross and microscopic, neither of us had any firsthand knowledge of the gross features of early human embryos. I had, however, learned from Dr. Chester Heuser his technique of searching for young stages of the macaque embryo.*

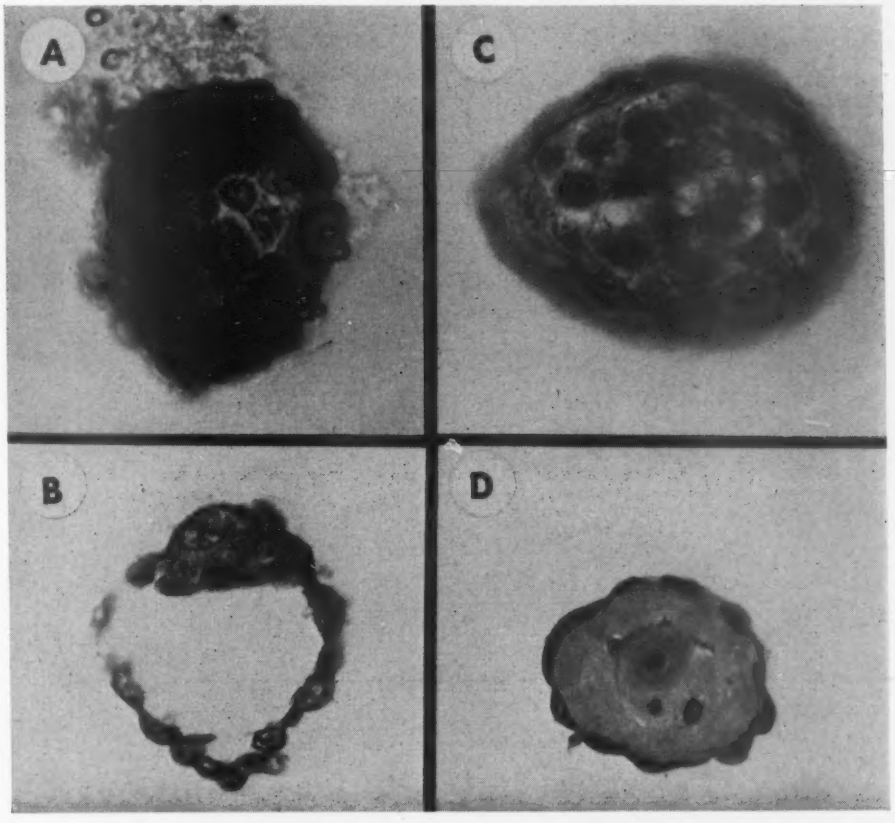


Fig. 8.—An intrauterine human blastocyst of about 4½ days (left) compared with an object presumably a detached endometrial polyp (right). Both are about the same size and gross appearance (top) but microscopic sections (below) reveal the true nature of each object. (All magnified about 400 diameters.)

A, Carnegie No. 8663, sequence 1. (From Contrib. Embryol. No. 240, 35: 199, 1954.)

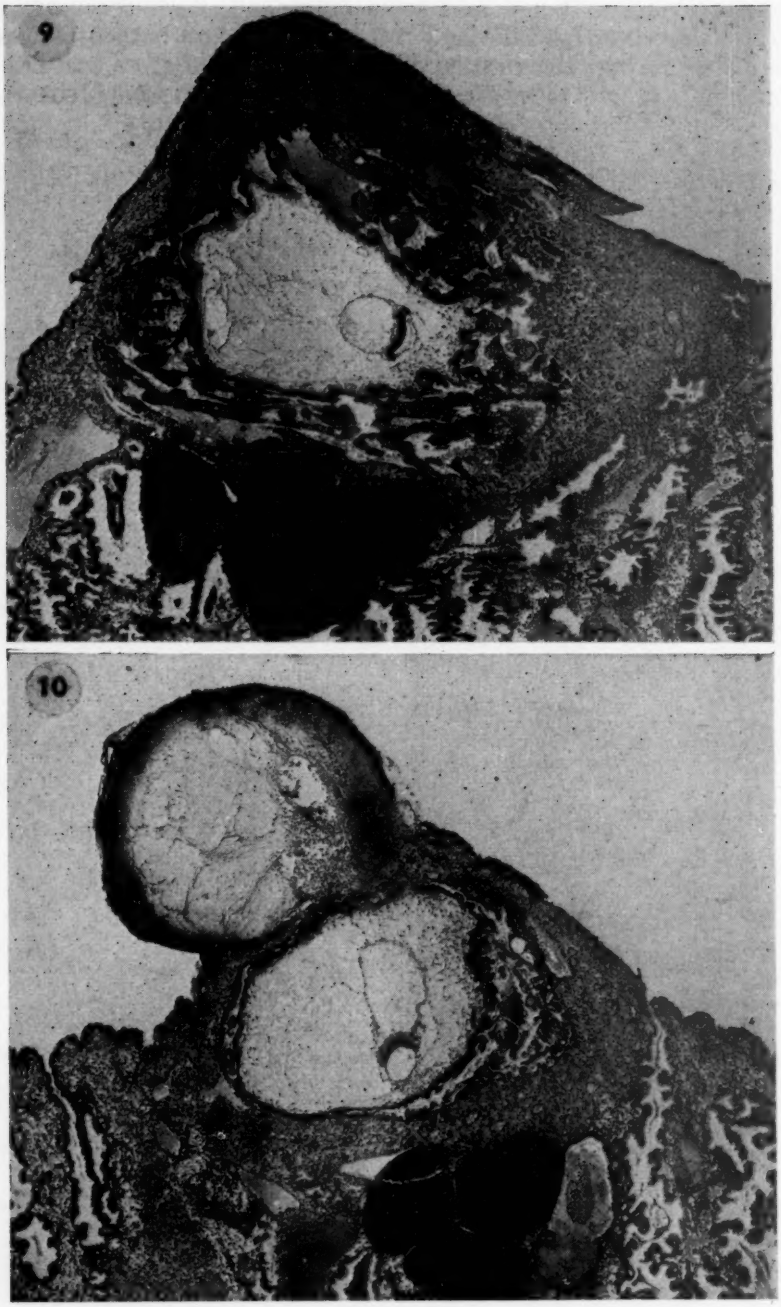
B, Carnegie No. 8663, section 9. (From Contrib. Embryol. No. 240, 35: 199, 1954.)

C, Carnegie No. 8330, sequence 4b.

D, Carnegie No. 8330, mid cross-section.

There were many artifacts encountered in tubal washings, as well as on, in, and beneath the surface of the endometrium, which we thought resembled early human conceptuses. It was naturally disappointing to have a detached polyp, resembling a blastula or a morula, disclose its true nature in microscopic sections. Equally frustrating were the sessile polyps, irregular contours of endometrial surfaces, and blocked endometrial glands which we thought and hoped were implantation sites. Whenever a particularly likely artifact came our way, the dictum of Carl Hartman, "If there is any doubt about it, t'aint

*Dr. Heuser, a distinguished embryologist and a master craftsman, aided by the mechanical genius of Mr. O. O. Heard, was entirely responsible for the technical excellence of the dissections and subsequent slides prepared from the human material sent from Boston. This technical perfection was complemented by Mr. Chester F. Reather's superb photography and Mr. James F. Didusch's artistic and technical skill in drawing the reconstructions prepared by Miss Eleanor C. Adams.



Figs. 9 and 10.—Two human pregnancies of about 13 days' developmental age to compare the normal (top) with the abnormal (bottom). (Both ×35; reduced ⅙.)

Fig. 9.—Note normal germ disk with well-developed amnion and definitive yolk sac. The embryo lies within a normal chorion whose early primordial villi are well developed and are just beginning to develop mesoblastic cores. The hemorrhage above and within the glands is normal. Carnegie No. 7801, Section 12-1-1. (From Contrib. Embryol. No. 201, 31: 85, 1945.)

Fig. 10.—This ovum is quite comparable in development except for marked hypoplasia of the trophoblast. This defect will result in a chorion whose villi will be insufficient to support embryonic life. Abortion will result. Carnegie No. 7800, Section 15-1-3. (From Hertig.[7])

an egg!'' stood us in good stead. Fig. 8, *A, B, C,* and *D,* illustrates a particularly handsome polypoid artifact and a true blastocyst with which it may be compared.

Surprising was the relatively high proportion of abnormal ova recovered from patients of known fertility. No local or general factors appeared to explain these potentially abortive ova other than the all-inclusive but nonspecific ''poor germ plasm'' proposed by Dr. Streeter. Thus, of the 34 ova recovered, 4 of the 8 free segmenting forms were abnormal, whereas only 6 of the 26 implanted ones were abnormal. Examples of a normal and abnormal ovum are seen in Figs. 9 and 10. This proportion and distribution of defective fertilized ova is, however, comparable to that throughout the animal kingdom—even in the primates—as seen in Fig. 11.

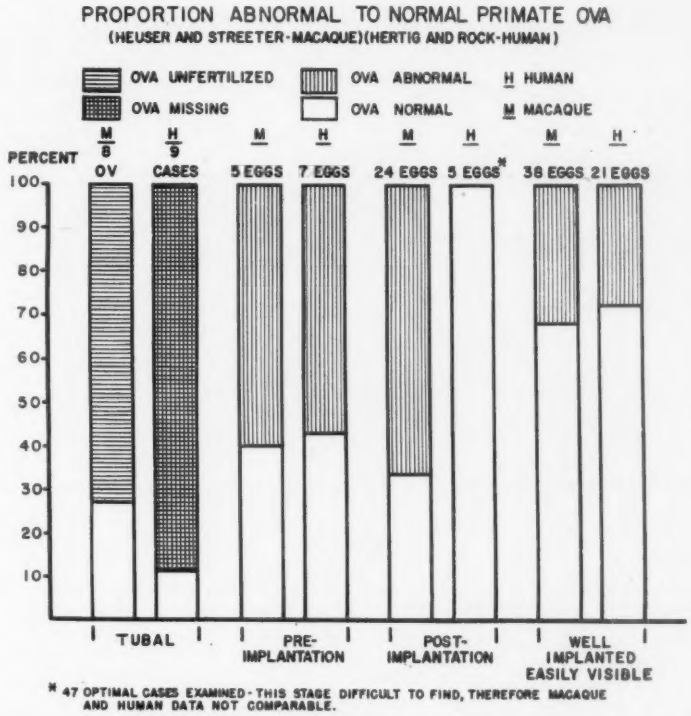


Fig. 11.—A comparison of the macaque and human ova during the first 17 days of development with respect to the proportion of those which are normal, abnormal, missing, or unfertilized.

Data presented by Hertig, A. T., before the Second Conference on Teratology, Bethesda, Maryland, April 17, 1957, as yet unpublished.

The morphologic aspects of the 34 conceptuses recovered from the 210 patients have all been illustrated and summarized in the George W. Corner Festschrift Volume of the *American Journal of Anatomy.*[12] This study may be briefly summarized as follows:

I. Of the 210 patients, 34 were pregnant, 73 were not pregnant in spite of optimal conditions, and 103 were also not pregnant because optimal conditions for fertilization were not possible.

II. Of the 73 patients in ''optimal'' condition, the failure to find an ovum might have been due to: (1) ease or difficulty of finding the specimen in patients scheduled for operation at a given stage of development (Fig. 12); (2) abnormality of the ovum with subsequent failure to be implanted; and (3) failure of the ovum to become fertilized.

III. Of the 36 patients in "optimal" condition whose endometria were 25 days old or older, 21 were pregnant (6 abnormal and 15 normal), whereas the other 15 were "perfect failures." Such "perfect failures" could again be ascribed to failure of fertilization or primary defectiveness of the fertilized zygote precluding implantation. Difficulty in finding the specimen was no longer a factor since the implanation site is over 0.5 mm. in diameter and grossly distinctive.

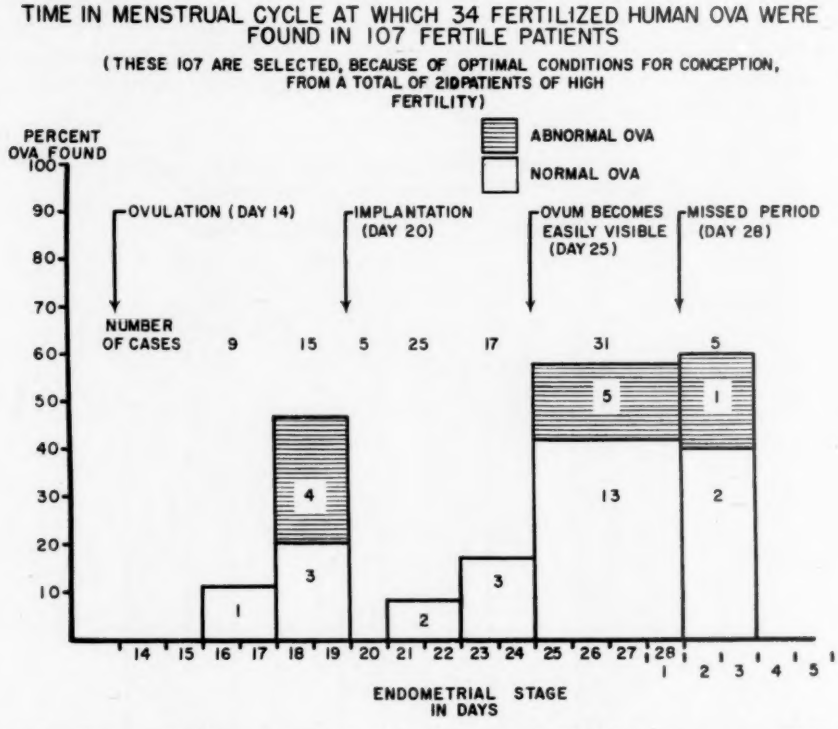

TIME IN MENSTRUAL CYCLE AT WHICH 34 FERTILIZED HUMAN OVA WERE FOUND IN 107 FERTILE PATIENTS
(THESE 107 ARE SELECTED, BECAUSE OF OPTIMAL CONDITIONS FOR CONCEPTION, FROM A TOTAL OF 210 PATIENTS OF HIGH FERTILITY)
PERCENT OVA FOUND
ABNORMAL OVA
NORMAL OVA
OVULATION (DAY 14)
IMPLANTATION (DAY 20)
OVUM BECOMES EASILY VISIBLE (DAY 25)
MISSED PERIOD (DAY 28)
NUMBER OF CASES 9 15 5 25 17 31 5
ENDOMETRIAL STAGE IN DAYS

Fig. 12.—The proportion of normal and abnormal fertilized human ova within the first 17 days of development. Also shown is the relative ease or difficulty of finding certain stages during this phase of development.

Data presented by Hertig, A. T., before the Second Conference on Teratology, Bethesda, Maryland, April 17, 1957, as yet unpublished.

Thus, under optimal conditions, the maximum chance of a fertile woman being clinically pregnant at the first missed period is 58 per cent, whereas the chance of having a normal conceptus at that time is only 42 per cent. The difference, 16 per cent, would appear to be the chance of producing a potentially abortive conceptus. Actually, of course, once the menstrual period has been missed, the chance of abortion is not 16 per cent but is of the order of 6 chances out of 21, or 28.6 per cent.

Aside from these data on clinical fertility, this study has confirmed, in general, the time of ovulation as lying within the period expressed by the formula, estimated ovulation time (E.O.T.) = 14 ± 2 days prior to the next expected menstrual period. This assumes an accurate knowledge of the patient's past menstrual history. Thus, in a cycle of 28 days, ovulation occurs about the fourteenth day. In long cycles, however, it occurs about 14 days prior to an expected period. As an example, one of our patients (Carnegie No. 8215, FHW S-43-2435), with long irregular cycles ranging from 27-55 days, apparently ovulated on the forty-sixth day as judged by the embryonic and endometrial development. In contrast, however, when cycles are short, ovulation occurs earlier in the cycle. Thus in another patient (Carnegie No. 8330,

FHW S 45-1823), the cycles ranged from 23 to 26 days, and ovulation apparently occurred on the eleventh day, again judging from embryonic and endometrial development.

Although we never found any implanting blastocysts, implantation must occur when the fertilized ovum is about 6 days old or in the seventh day of development. Thus, the associated endometrium is equivalent to that of the normal twentieth day (6 + 14 = 20).

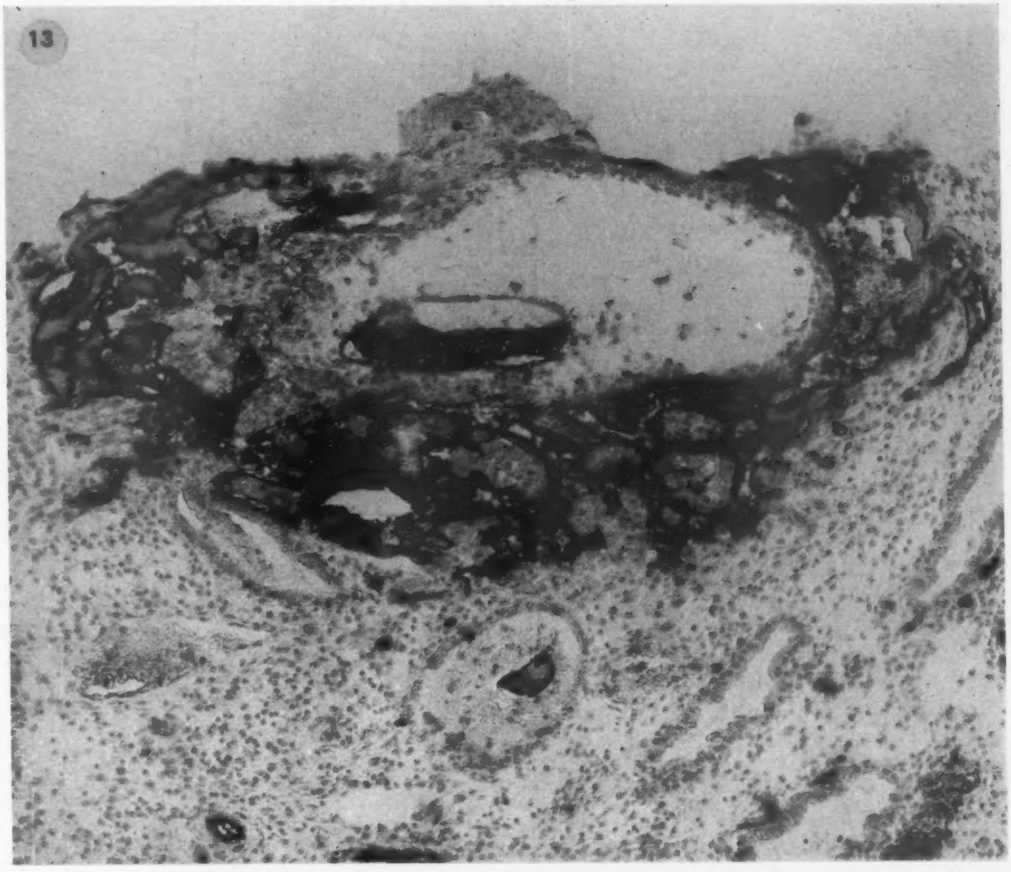


Fig. 13.—An early villous human ovum of about 13 days' developmental age reacted for alkaline phosphatase. Note concentration of the enzyme in the ecto- and entoderm of the germ disk and also within the syncytiotrophoblast of the primordial villi. The maternal blood vessels also react positively for this enzyme. Fetus 55, FHW S-54-3305. (×110; reduced 2/7.)

No mention need be made here of the morphologic aspects of early human development from the second to the seventeenth day. The reader is referred to previously published papers, all listed in reference No. 12.

Research by Younger Colleagues

In 1950, when I became Chairman of the Department of Pathology at Harvard, Dr. Donald G. McKay* became actively associated with the research program as it involved obstetric and gynecologic pathology.

*Dr. McKay was trained at the Mallory Institute of Pathology and in connection with that training was a former resident in pathology at the Boston Lying-in Hospital and the Free Hospital for Women. He is now Pathologist to the Free Hospital for Women and a Visiting Pathologist to the Boston Lying-in Hospital, having at one time been pathologist to both hospitals.

The search for early human ova continued and McKay and Miss Eleanor C. Adams launched an extensive program of studying serially sectioned older embryos by various histochemical means. We were fortunate enough, however, to find a normal 13 day villous specimen which Miss Adams serially sectioned and reacted histochemically or stained for various special substances. This specimen has been reported upon briefly before the American Association of Anatomists[13] and is to be described fully for publication in this JOURNAL in connection with the 1958 meeting of the American Gynecological Society.

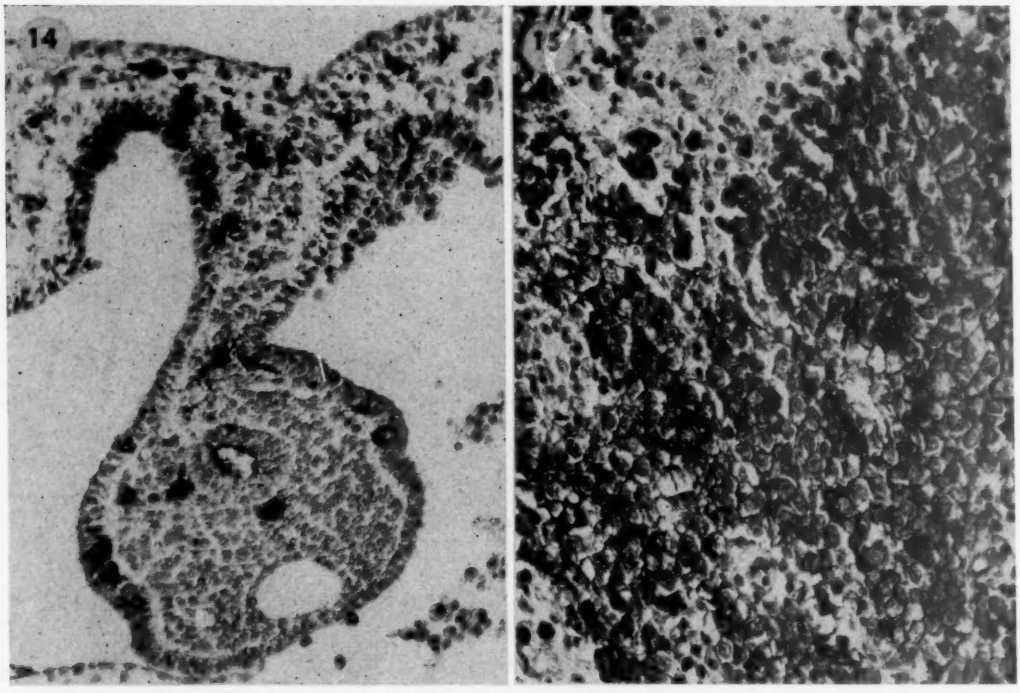


Fig. 14.—Gut, mesentery, and region of future gonad from normal human 5 mm. embryo reacted for alkaline phosphatase. Note concentration of enzyme in primordial germ cells which are in act of migrating to their ultimate position in the gonad. Fetus 5, FHW S-52-1019. (From original of Fig. 2, McKay, Hertig, Adams, and Danziger: Anat. Rec. 117: 208, 1953.) (×200; reduced ⅙.)

Fig. 15.—Dysgerminoma of human ovary reacted for alkaline phosphatase. Note similarity of reaction of tumor cells to that of primordial germ cells, indicating nature of cell type in the tumor. St. Elizabeth's Hospital, Boston, E-50-614. (From original of Fig. 9, McKay, Hertig, Adams, and Danziger: Anat. Rec. 117: 217, 1953.) (×200; reduced ⅙.)

One of the cross sections through the mid-ovum, reacted for alkaline phosphatase, is seen in Fig. 13. It may be compared with a similar specimen shown in Fig. 9, fixed and stained by conventional methods. The great concentration of this enzyme in the syncytiotrophoblast and embryonic germ disk is probably related to the great functional activity and growth in those respective tissues. These newer methods are attempts at a better correlation of form and function in a rare tiny object which cannot reasonably be subjected to the more destructive methods of biochemistry, desirable though the chemical data from such experiments might be.

Several papers[14, 15, 16] have resulted from the histochemical investigation of embryos at various stages of development. This technique has thrown some light on the old anatomic debate concerning the origin of the primary germ cells.[14] One group favors the origin from "germinal" epithelium whereas the other (including our group) believes that germ cells arise at some early stage

of development. Subsequent active migration and passive transport by growth and development of endodermal structures result in their deposition in the primordial gonad. Histochemical evidence for this thesis is seen in Fig. 14.

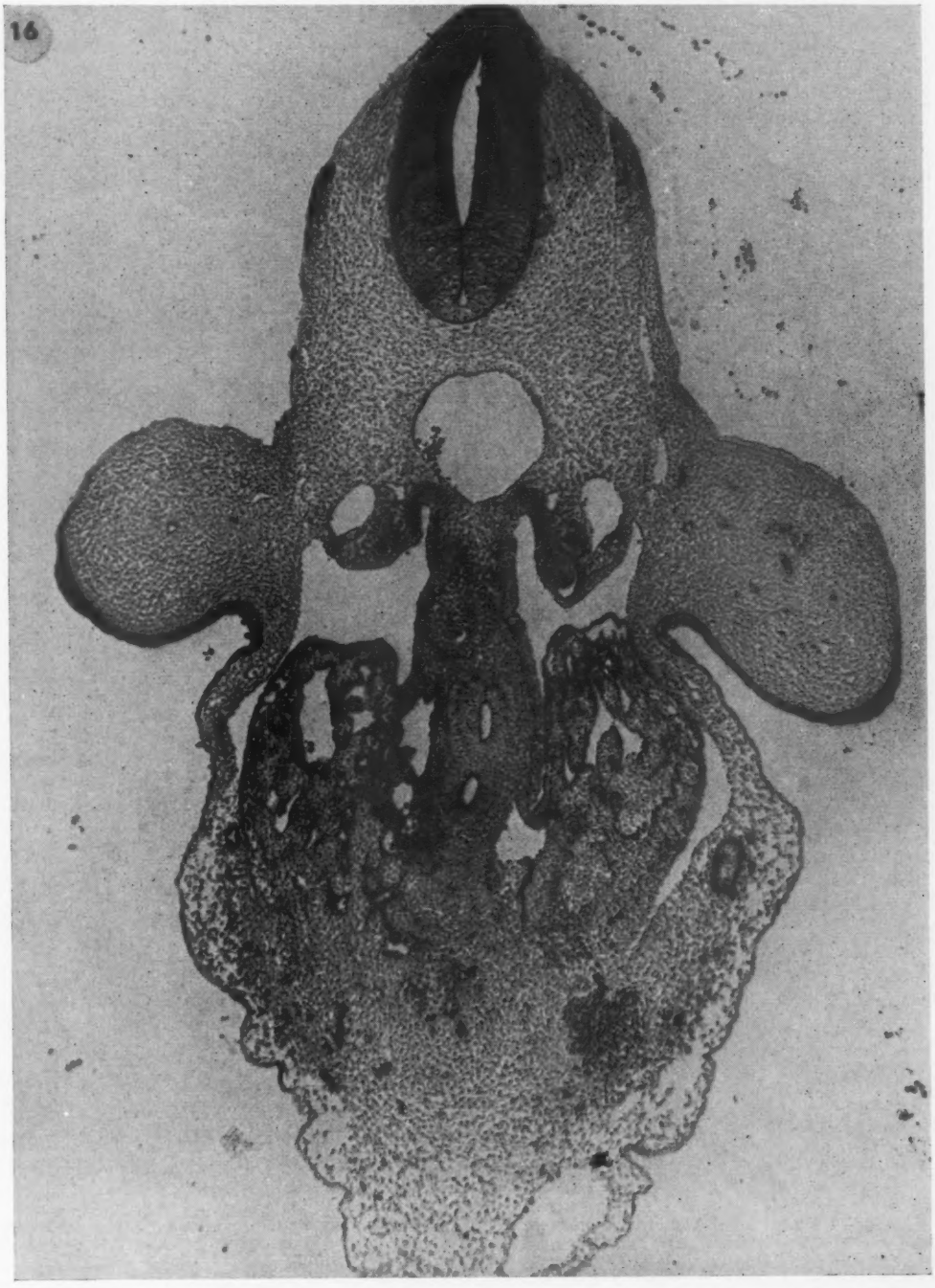
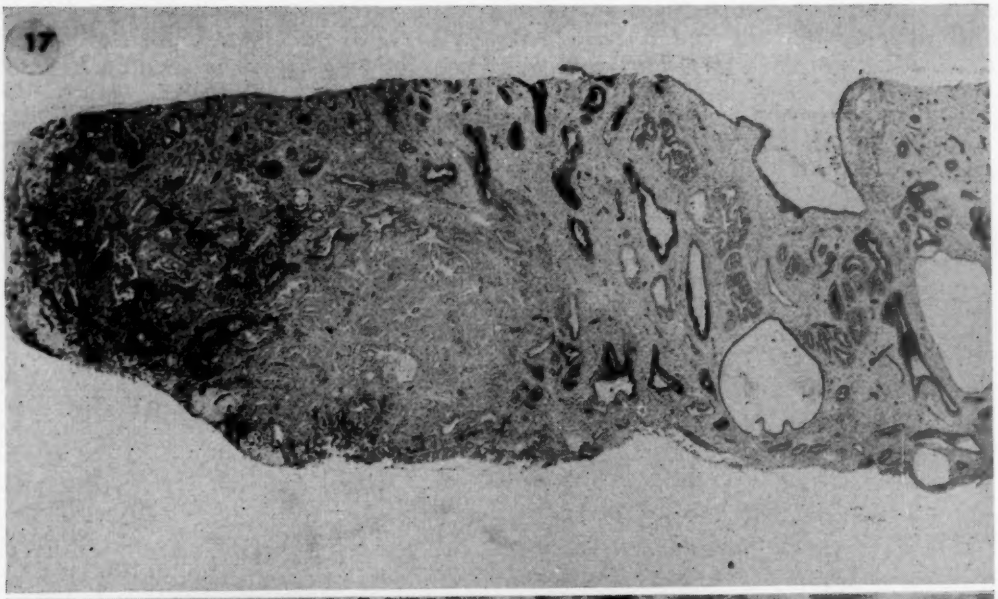
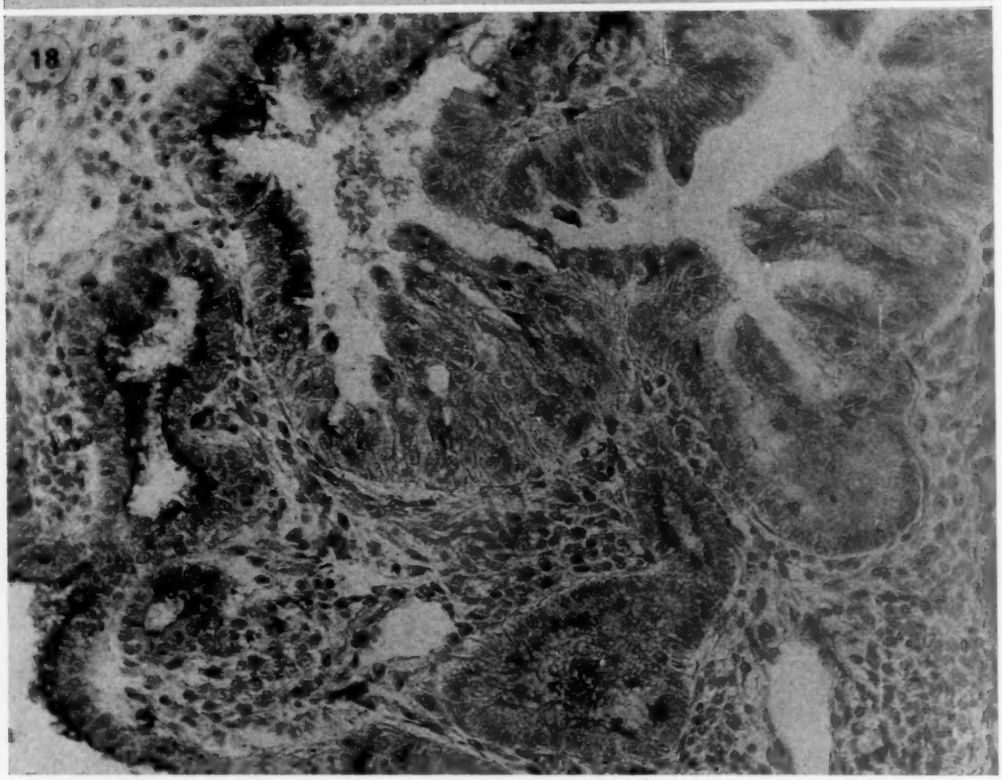


Fig. 16.—Cross section of 6 mm. human embryo through neural tube, anterior limb bud, urogenital ridge, and liver, reacted for alkaline phosphatase. Note concentration of enzyme in neural tube, tip of limb bud, "germinal" epithelium at angle of gonadal ridge and gut mesentery, and sinusoids of liver. These sites all indicate regions of growth or interfaces where active exchange of materials is taking place. Fetus 33. FHW S-53-1910. (From original of Fig. 1, McKay, Adams, Hertig, and Danziger: Anat. Rec. 126: 451, 1956.) (× about 95; reduced ⅙.)

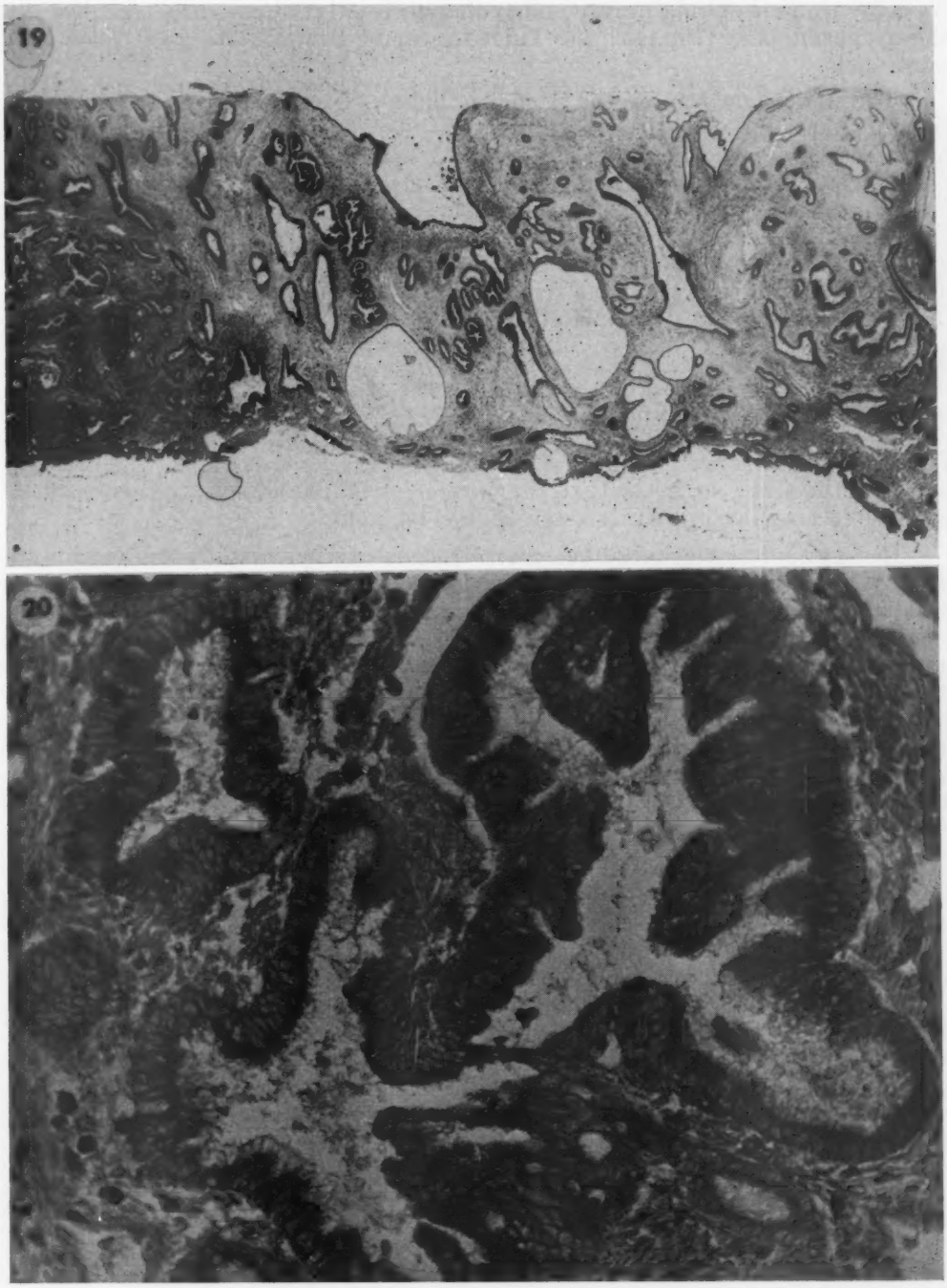




Figs. 17 and 18.—Alkaline phosphatase of endometrium showing focus of carcinoma in situ. Same specimen as that shown in Figs. 19 and 20. (From McKay, Hertig, Bardawil, and Velardo: Histochemical Observations on the Endometrium. II. Abnormal Endometrium, Obst. & Gynec. 8: 140, 1956.)

Fig. 17.—Low-power view to show focus of early neoplasia (pale) and to contrast the latter with the proliferative glands which contain the enzyme. FHW S-52-656. (×7; reduced ⅙.)

Fig. 18.—High-power view of one gland from focus seen in Fig. 17, to show the alkaline phosphatase still remaining in the better-differentiated portion of the gland on the left and the absence of the enzyme in the less well-differentiated epithelium on the right. FHW S-52-656. (×260; reduced ⅙.)



Figs. 19 and 20.—Acid phosphatase of endometrium showing a focus of carcinoma in situ. Same specimen as that shown in Figs. 17 and 18. (From McKay, Hertig, Bardawil, and Velardo: Histochemical Observations on the Endometrium. II. Abnormal Endometrium, Obst. & Gynec. 8: 140, 1956.)

Fig. 19.—Note dark focus of early neoplasia on the left and contrast with lower concentration of enzyme in remaining normal glands. See Fig. 20 for higher-power detail of one gland from this focus; the same gland being shown in Fig. 18 but reacted for alkaline phosphatase. FHW S-52-656. (×7; reduced ⅙.)

Fig. 20.—Higher-power detail of gland from focus seen in Fig. 19. Note less concentration of enzyme in better-differentiated epithelium on left and greater concentration in less well-differentiated epithelium on right. FHW S-52-656. (×260; reduced ⅙.)

As a by-product of this purely embryologic investigation, it became clear that the dysgerminoma (Fig. 15) was indeed a tumor recapitulating the primordial germ cells.

The histochemistry of the 5 mm. human embryo[15] again showed correlation of form and function; alkaline phosphatase was concentrated at membrane interfaces and in rapidly growing tissues. Thus, this enzyme was localized on surfaces separating maternal plasma from chorionic fluid, chorionic fluid from embryonic venous plasma, and embryonic arterial plasma from embryonic intercellular fluid. The association of alkaline phosphatase with growth is shown by its concentration in the neural tube, limb buds, gut tract, dorsal portion of liver, and the trophoblast. The inorganic phosphate appears to be involved in the synthesis of nucleoproteins. At this stage, as shown by glycogen stains, the yolk sac functions as a "preportal" unit, the metabolic deficiencies of the liver being made up by the yolk sac.

These findings were confirmed and amplified in the 6 and 7 mm. stage.[16] Fig. 16 shows a section of a 6 mm. specimen reacted for alkaline phosphatase. The presence of large amounts of glycogen in the yolk sac and its virtual absence in the liver suggests that the former structure supplies glucose to the embryonic circulation at this stage of development.

McKay and co-workers have completed an extensive study (as yet unpublished) of all stages of trophoblast by histochemical methods. The primitive cytotrophoblast matures into 5 types: Langhans, cell columns, placental septa, placental site giant cells, and that of the chorion laeve. Each has a significantly different histochemical pattern which is presumably correlated with its metabolic function as well as its anatomic location. The capillary basement membrane of the chorionic villi begins to thicken at about the thirty-sixth week, which could account for reduction in placental efficiency as term is approached and passed. These observations may help to explain fetal deaths in the postmaturity syndrome.

Dr. John M. Pinkerton (Rockefeller Research Fellow on "loan" from the Department of Obstetrics and Gynecology of the University of the West Indies, Jamaica) and McKay have traced the development of the human ovary from that of the 3.7 mm. embryo to that of the 15-year-old child. These data have been prepared but as yet are unpublished. They showed that the primordial germ cells, characterized by containing large amounts of glycogen and alkaline phosphatase, may be divided into 3 phases of development: (a) migration up to the eighth week, (b) proliferation up to the twentieth week, and (c) maturation from the twentieth to the twenty-eighth week, when most primordial follicles have been formed. Many of the oocytes undergo atresia progressively from this embryonic stage throughout childhood. Celomic mesoblast supplies mesenchymal cells to the underlying gonad until the fifteenth week and possibly later, until the surface epithelium and basement membrane are formed during the last trimester. The tunica albuginea, forming during childhood, further separates the gonad from the surface epithelium. The granulosa cells are derived from mesenchymal cells which, in part at least, are derived from surface celomic epithelial cells. The ovarian cortical stroma is derived from the connective tissue accompanying the hilar blood vessels.

A tissue culture laboratory has been established to grow benign and malignant trophoblast. This has been organized and directed by Dr. Wadi A. Bardawil, who is investigating the problem of trophoblastic regression. In studies, using placental tissue subjected to the Coons' fluorescent antibody technique to test for the presence of antitrophoblastic antibodies in the pregnant patient, he discovered that the positive results were in some way related to the fact that the patient had scleroderma. Further investigation showed that other

"collagen diseases" such as disseminated lupus erythematosus and dermatomyositis show this sensitization to desoxyribonucleoprotein,* another example of "chance favoring the mind which is prepared"!

The problems of gynecologic pathology have not been neglected in the application of newer techniques. Earlier researches on the morphologic precursors of endometrial carcinoma by Dr. Sheldon C. Sommers and others[17, 18, 19] in the laboratory indicated a gradual transition of the endometrium during the 15 years preceding the development of carcinoma. These various hyperplasias and atypia culminated in so-called carcinoma in situ a few years before true invasive carcinoma developed.

Histochemical investigation of normal[20] and abnormal[21] endometria was undertaken in 1950. These studies showed that these early morphologic changes of malignancy lose the reactions characteristic of proliferative endometrium and take on those of secretory endometrium (Figs. 17 to 20). This suggested to McKay that perhaps both estrogenic and progesteronic substances in some way influenced the development of endometrial carcinoma.

In 1952, Dr. Kurt Benirschke** became associated with the research work here being summarized. His chief interests are those of perinatal mortality and fetal endocrinology. The steroid studies, in conjunction with Bloch, on the function of the fetal adrenal cortex showed that C_{19} steroidogenesis is limited to the fetal cortex whereas C_{21} steroid production occurs in the definitive cortex. This work suggests that chorionic gonadotrophins were responsible for the maintenance of the fetal cortex during the first 20 weeks, whereas the luteinizing hormone from the fetal pituitary, stimulated by chorionic estrogens, is believed to be responsible after that time.[22]

At the Boston Lying-in Hospital long-term studies on the changes in the cervix in pregnancy continue. It is hoped that they may shed some light on the relation of endocervical eversion, erosion, and metaplasia to the histogenesis of carcinoma in situ. These studies begun under the immediate supervision of Dr. Crawford W. Hinman are now being carried on by Dr. Lorna D. Johnson.

Meanwhile, the histologic criteria of carcinoma in situ have been prepared for publication by Dr. Gilbert H. Friedell, using the extensive material at the Free Hospital for Women. These studies are an extension of those begun many years ago by Dr. Paul A. Younge.[23]

Much of the experience gleaned from the diagnostic routine and research work in the pathology laboratories of the Boston Lying-in Hospital and Free Hospital for Women during the past 26 years is embodied in a chapter written in collaboration with Dr. Hazel Mansell for Anderson's third edition of his text on pathology.[24]

The department of pathology has recently been given permission by the United States Public Health Service to acquire an electron microscope. This instrument should make it increasingly easier to interpret the normal and abnormal morphology in terms of normal or abnormal physiologic processes.

Summary

An attempt has been made to show how a research program in pathology dictated by the problems and material of an obstetric and a gynecologic hospital has evolved over a quarter of a century. Effort has always been made to correlate form and function with the use of new techniques as they appear.

*Submitted for publication.

**Dr. Benirschke was trained in pathology at the Peter Bent Brigham Hospital, the Children's Hospital, and the Boston Lying-in Hospital. He is at present the Pathologist of the latter hospital.

Any past work is merely preparation for the future as expressed so succinctly by Shakespeare when he had Antonio say, "Whereof what's past is prologue."[25]

References

1. Gilmer, P. M.: J. Parasitol. **10**: 80, 1923.
2. Gilmer, P. M.: Ann. Ent. Soc. America **18**: 203, 1925.
3. Hertig, A. T., and Hertig, M.: Science **65**: 328, 1927.
4. Smith, R. O. A., Halder, K. C., and Ahmed, I.: Indian J. M. Research **28**: 575, 581, 585, 1940; **29**: 783, 799, 1941.
5. Bacot, A. W., and Martin, C. J.: J. Hyg. (Plague Supplement III) **13**: 423, 1914.
6. Hertig, A. T.: Contrib. Embryol. **25**: 38, 1935.
7. Hertig, A. T.: Yale J. Biol. & Med. **18**: 107, 1945.
8. Hertig, A. T., and Edmonds, H. W.: Arch. Path. **30**: 260, 1940.
9. McKay, D. G., Roby, C. C., Hertig, A. T., and Richardson, M. V.: Am. J. Obst. & Gynec. **69**: 722, 735, 1955.
10. Hertig, A. T., and Sheldon, W. H.: Am. J. Obst. & Gynec. **53**: 1, 1947.
11. Hertig, A. T., and Mansell, H.: In Atlas of Tumor Pathology, Washington, D. C., 1956, Armed Forces Institute of Pathology, sec. 9, fasc. 33.
12. Hertig, A. T., Rock, J., and Adams, Eleanor: Am. J. Anat. **98**: 435, 1956.
13. Hertig, A. T., Rock, J., Adams, E. C., and Mulligan, W. J.: Anat. Rec. **127**: 306, 1957. (Abstract.)
14. McKay, D. G., Hertig, A. T., Adams, E. C., and Danziger, S.: Anat. Rec. **117**: 201, 1953.
15. McKay, D. G., Adams, E. C., Hertig, A. T., and Danziger, S.: Anat. Rec. **122**: 125, 1955.
16. McKay, D. G., Adams, E. C., Hertig, A. T., and Danziger, S.: Anat. Rec. **126**: 433, 1956.
17. Hertig, A. T., and Sommers, S. C.: Cancer **2**: 946, 1949.
18. Sommers, S. C., Hertig, A. T., and Bengloff, H.: Cancer **2**: 957, 1949.
19. Hertig, A. T., Sommers, S. C., and Bengloff, H.: Cancer **2**: 964, 1949.
20. McKay, D. G., Hertig, A. T., Bardawil, W. A., and Velardo, J. T.: Obst. & Gynec. **8**: 22, 1956.
21. McKay, D. G., Hertig, A. T., Bardawil, W. A., and Velardo, J. T.: Obst. & Gynec. **8**: 140, 1956.
22. Benirschke, K., Bloch, E., and Hertig, A. T.: Endocrinology **58**: 598, 1956.
23. Hertig, A. T., and Younge, P. A.: Am. J. Obst. & Gynec. **64**: 807, 1952.
24. Hertig, A. T., and Mansell, H.: In Anderson, W. A. D.: Pathology, St. Louis, 1957, The C. V. Mosby Company, chap. 39, p. 1032.
25. Greene, Herbert E., editor: The Tudor Shakespeare. New York, 1922, The Macmillan Company, The Tempest, Act II, Scene 1, line 253.

PROGESTERONE-INDUCED WITHDRAWAL BLEEDING AS A SIMPLE PHYSIOLOGIC TEST FOR PREGNANCY*

GLEN E. HAYDEN, M.D., CHICAGO, ILL.

(From the Department of Obstetrics and Gynecology of the University of Chicago and the Chicago Lying-in Hospital

ONE of the major diagnostic problems constantly presented to the clinician is the differentiation of early pregnancy from secondary amenorrhea of short duration. There are numerous pregnancy tests but none approaches 95 to 100 per cent accuracy and few are applicable early in pregnancy. There is little question that when a specific test for pregnancy is needed the Aschheim-Zondek[1] or Friedman[2] test is fairly reliable, as are the toad and frog tests of Weisman and Coates,[3] and Galli-Mainini.[4] These tests are essential to meet the needs of accurate diagnosis and cannot be replaced by tests which fall into the classification of physiologic phenomena. The disadvantages are that the tests are not uniformly accurate, especially in early pregnancy, and that they require costly laboratory facilities.

Tests based on physiologic phenomena are becoming increasingly important as our understanding of physiology increases, as the various agents needed become available, and as the cost factor is overcome. Examples of this type of test are the neostigmine methylsulfate[5] or estrone test[6] to induce withdrawal bleeding, the failure to produce bleeding being a positive sign. The use of progesterone as a diagnostic and therapeutic agent in the management of amenorrhea has been evaluated,[7-11] and the application of progesterone-induced withdrawal bleeding as a diagnostic test for pregnancy has been employed with surprising accuracy. Hady Gediz[12, 13] employed intramuscular and intrauterine progesterone for the differential diagnosis of amenorrhea and pregnancy with 100 per cent accuracy. Caffier[14] and Hayden[15] both have confirmed the unusual accuracy of this test.

The use of progesterone in the diagnosis of early pregnancy is predicated on its ability to induce withdrawal bleeding in patients with proliferative or estrogen-prepared endometrium. The application of this method to the differentiation of pregnancy from other causes of amenorrhea is necessarily based on the premise that one of the three principal structures, namely, uterus, ovaries, or pituitary, may be responsible for the amenorrhea. Menstruation after progesterone therapy in a patient with amenorrhea indicates that the

*Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

pituitary must be in a more or less normal functional status, since it is producing sufficient follicle-stimulating hormone to cause the ovary to secrete sufficient estrogenic hormone. Finally, the endometrium must be capable of responding and developing to the point of proliferative endometrium. Hence, the patient has a comparatively normal genitoendocrine system. In the absence of proliferative endometrium, as with decidua or the undeveloped endometrium of premenarche or the atrophy of the menopause, no withdrawal bleeding will occur.

This study has been designed to demonstrate that, in the patient with previously regular menstrual cycles, progesterone agents, by any of three modes of administration, offer a safe physiologic method of inducing withdrawal bleeding to differentiate early pregnancy from secondary amenorrhea of short duration.

Procedure

One hundred and twenty patients were selected only on the basis of previously regular menstrual periods and the distinct possibility that a conception had occurred. The age range was limited to 18 to 35 years. The patients were instructed to report any unusual bleeding and to bring in any clots or tissue passed. All the patients were amenorrheic for 35 to 70 days from the first day of the last menstrual period. The medication was given to 102 patients according to one of the following three modes of administration:

1. Anhydrohydroxyprogesterone was given orally in a dose ranging from 200 to 400 mg. per day for 4 to 5 days.

2. Progesterone U.S.P. was administered vaginally in a dose ranging from 75 to 250 mg. per day for 4 to 5 days.

3. 17-alpha-hydroxyprogesterone caproate was injected intramuscularly in doses of 125 to 500 mg. per day for 2 to 5 days.

Results

Following this procedure one of two results occurred, as may be anticipated, namely, withdrawal bleeding did or did not ensue within 14 days. As shown in Table I, 102 patients received progestogens according to the above scheme. Sixty-four patients failed to respond and a gestation was confirmed in each instance. All the pregnancies continued uneventfully and normal term infants resulted. In 38 cases withdrawal bleeding occurred. With the oral and vaginal administration the onset of withdrawal bleeding in 23 of 27, or 85 per cent of the patients, began between the third and the seventh days from the day of cessation of medication. The intramuscular administration produced a longer time interval, as was expected. The onset occurred between the eighth and the fourteenth days in 8 out of 11 patients and the interval was as long as 16 days in one individual. The withdrawal bleeding, or induced menstruation, was evaluated on the basis of amount and duration in comparison with the individual patient's normal menstrual period (Table II). Twenty-six, or 68 per cent, reported that the type, amount, and duration of bleeding were as would be expected with a normal menstrual period. Only 6 patients reported either excessive amounts or prolonged duration of bleeding, but none of the patients required hospitalization for control of the bleeding. In 6 cases the bleeding was scanty and of short duration, but the bleeding always exceeded 2 days. Although 8 or more patients brought in suspicious

specimens, examination revealed only blood clots and no tissue or decidua-like casts were obtained. The amount and duration of bleeding could not be correlated with the mode of administration or amount.

TABLE I. PROGESTERONE INDUCED MENSES

	NO MENSES, NO RESPONSE. PREGNANT	ARTIFICIAL MENSES. NOT PREGNANT	TOTAL	DAYS TO ONSET OF WITHDRAWAL BLEEDING		
				3-7	8-13	14+
Oral. Anhydrohydroxyprogesterone (Ethisterone) 200 mg. for 4 to 5 days	27	17	44	15	2	0
					(85% between 3 and 7 days)	
Vaginal. Progesterone, U.S.P. 75 to 250 mg. for 4 to 5 days	33	10	43	8	2	0
Intramuscular. 17-α-hydroxyprogesterone caproate 125 to 500 mg. for 2 to 4 days	4	11	15	2	8	1
Total	64	38	102			

TABLE II. WITHDRAWAL BLEEDING; COMPARATIVE RESPONSE

	COMPARISON OF WITHDRAWAL BLEEDING TO NORMAL MENSES			TOTAL
	SCANTY	NORMAL	PROFUSE*	
Oral. Anhydrohydroxyprogesterone (Ethisterone) 200 mg. for 4 to 5 days	3	12	2	17
Vaginal. Progesterone, U.S.P. 75 to 250 mg. for 4 to 5 days	2	7	1	10
Intramuscular. 17-α-hydroxyprogesterone caproate 125 to 500 mg. for 2 to 4 days	1	7	3	11
Total	6	26 (68%)	6 (16%)	38

*No hospitalization required for control.

The amenorrhea of the nonpregnant group must then be classified as secondary, but probably a better term, namely, functional, as suggested by Greenblatt,[11] would be more appropriate and desirable, since the duration of the amenorrhea was extremely short. No follow-up could be obtained in 2 instances, but 4 to 6 months' follow-up examinations were available in 36 cases (Table III). Twenty-six patients, or 72 per cent, returned to normal menstrual cycles and no further evaluation or therapy was indicated or needed. All but one of these patients were university students and 80 per cent were between the ages of 18 and 24 years. Ten patients failed to return to normal menstrual cycles within 40 days from the time of the induced menstrual period. A routine evaluation was performed on each patient and consisted of a general physical and pelvic examination, cytologic diagnosis, basal metabolic rate determination, endometrial biopsy, skull x-ray examination, and 17-ketosteroid determinations. Two patients were under psychiatric evaluation during the time of the episode of amenorrhea. Empirically, all patients were placed on thyroid medication in doses ranging from 30 to 60 mg. daily regardless of the basal metabolism rates, all of which were within the limits of normal. All patients were considered normal by examination

but 2 patients had a moderate nutritional type of obesity. No adrenogenital syndromes were present in this group and subsequent urinary studies confirmed the clinical evaluation. Four patients developed normal menstrual cycles after 30 to 50 days of thyroid therapy and 3 patients began having irregular menstrual cycles, ranging from 35 to 45 days. In all of these 7 patients the menstrual periods returned to normal in amount, duration, and type of bleeding. Three patients left after 4 months, but no regular menstrual cycles had been established and a complete evaluation was not possible. The mode of the original progesterone medication in no way influenced the eventual re-establishment of normal menstrual cycles.

TABLE III. FOLLOW-UP APPRAISAL OF THERAPEUTIC VALUE

	RETURNED TO NORMAL	IRREGULAR FOR REGULAR DIAGNOSIS	TOTAL
Oral. Anhydrohydroxyprogesterone (Ethisterone) 200 mg. for 4 to 5 days	13 (1 unknown)	3	17
Vaginal. Progesterone, U.S.P. 75 to 250 mg. for 4 to 5 days	6	4	10
Intramuscular. 17-α-hydroxyprogesterone caproate 125 to 500 mg. for 2 to 4 days	7 (1 unknown)	3	11
Total	26 (72%) (2 unknown)	10 (28%)	38

The Use of Excessively Large Doses of Progesterone

In 18 cases, 1,000 mg. or more per day was administered with the aim of determining whether progesterone therapy could in any way alter the course of a normal gestation. There was no reason to assume that a gestation would be disturbed, and in the 14 normally pregnant patients the gestations continued uneventfully. As shown in Table IV, in one instance the patient had bleeding and pains prior to the start of the intramuscular medication, but by the end of the therapy the bleeding had subsided and the pregnancy continued normally for an additional 6 to 7 weeks. Subsequently, at 18 to 20 weeks, the bleeding and pain recurred and a spontaneous abortion took place. The fetus was found to be normal in development, and its size was compatible with the gestational dates. The time interval was considered too great to assume that the progesterone therapy in any way altered the eventual outcome, except beneficially.

In 3 instances withdrawal bleeding resulted. In the first case a diagnostic dilatation and curettage was performed as soon as bleeding occurred and microscopic examination showed secretory endometrium and no chorionic villi. In the other 2 instances, as shown in Table IV, the withdrawal bleeding began and continued as a normal menstrual period; no tissue or clots were passed by one patient, but the other passed clot and tissue. Grossly, the specimen resembled a decidua-like cast and microscopically this was confirmed. In addition, the Friedman tests were negative.

In 12 cases the basal body temperature was recorded and with the additional excessive doses no elevation was noted.

The extraction of pregnanediol from 24 hour urine collections was performed in 8 cases. By our laboratory standards the peak levels of the normal menstrual cycle ranged from 5 to 8 mg. per 24 hour specimen. As shown in Fig. 1, regardless of the mode of administration, all methods and agents produced effective elevations in urinary pregnanediol, which would indicate a

therapeutic activity by the various progesterone agents. Interestingly, the 3 nonpregnant patients showed an initial level of pregnanediol within normal limits of a menstrual cycle in the luteal phase and the 5 pregnant patients had 5 or more mg. per 24 hours. Four of the 5 pregnant patients showed a sharp decrease in the pregnanediol level by the twelfth to the fourteenth day but the course of the gestations was unaltered.

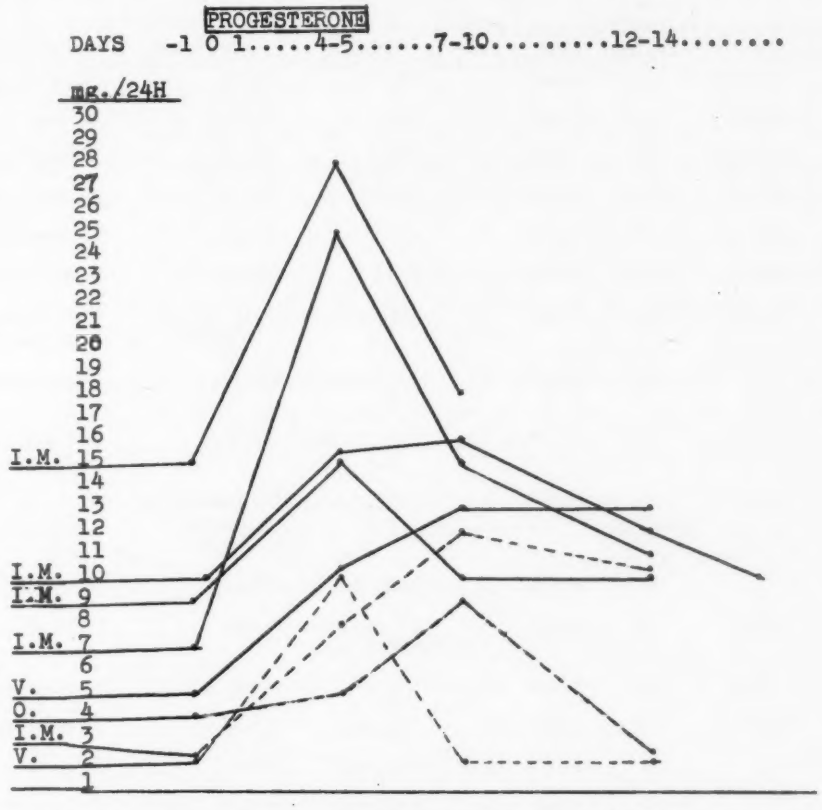


Fig. 1.—Relationship of urinary pregnanediol (milligrams per 24 hours) to mode of administration and time. Nonpregnant patients indicated by broken lines.

Comment

The greatest advantage of this method of management is the fact that no laboratory equipment, animals, or specimens are needed. Since the oral and vaginal modes of administration are equally as effective as the intramuscular, there is no need for injection or frequent office visits. In addition, the oral or vaginal progestogens induce a far more rapid onset of withdrawal bleeding. One may speculate that if ovulation occurred during the medication the onset of bleeding would be delayed up to 14 or more days.

There were no undesirable side reactions. In fact, the progestogens are probably among the safest medications available to use in either the pregnant or nonpregnant patient. The therapeutic value was of major importance since normal, regular menstrual cycles were restored in 72 per cent of the amenorrheic patients. Thus, because of its diagnostic as well as therapeutic value, progesterone will undoubtedly become even more extensively used in amenorrhea, especially when the time and medical expense necessary to evaluate this

type of case are considered. In the patient with prolonged secondary amenorrhea, however, this approach should not be part of the initial step. A thorough diagnostic workup is essential before this therapy is undertaken. This method is designed primarily for the brief or functional type of amenorrhea.

TABLE IV. PROGESTERONE TEST WITH EXCESSIVE DOSAGE

INITIAL	UNIT NO.	WEEKS OF GESTATION	DOSE (MG.)	NO. OF DAYS	ROUTE	RESPONSE	END RESULT
A. B.	448534	6-8	1,000	5	Oral	None	Normal gestation
C. M.	660255	6-8	1,000	5	Oral	None	Normal gestation
A. M.	506867	6+	2,000	5	Oral	None	Normal gestation
J. L.	510132	6+	2,000	5	Oral	None	Normal gestation
J. G.	506736	6-8	2,000	5	Oral	None	Normal gestation
E. M.	506606	6-8	1,000	5	Oral	None	Normal gestation
B. J.	541647	6-8	1,250	5	Intramuscular	16½ days, bleeding	Curettage. Decidua-like cast
N. A.		6-8	1,250	4	Intramuscular	None	Normal gestation
B. T.		6-8	1,250	4	Intramuscular	None	Normal gestation
J. H.	539051	10+ Bleeding	1,250	4	Intramuscular	Stopped bleeding for 8 weeks	At 18-20 weeks, complete abortion
B. P.		8+	4,000	5	Vaginal	None	Normal gestation
R. M.	509065	6-8	1,000	5	Intramuscular	None	Normal gestation
P. M.	660694	6-8	2,000	5	Vaginal	None	Normal gestation
C. McL.	550266	6-8	5,000	5	Vaginal	None	Normal gestation
E. (M) N.		6+	2,500	5	Vaginal	None	Normal gestation
N. C.		6+	3,000	5	Vaginal	6 days, bleeding and tissue	Friedman test negative. Decidua-like cast
M. B.	530534	6-8	3,500	5	Vaginal	6 to 8 days, brownish discharge	Normal gestation
A. N.	501320	6-8	1,000	5	Oral	3 days, bleeding, not pregnant	No tissue, no clots

In 4 of the 5 pregnant patients the urinary pregnanediol levels decreased sharply but remained within the normal limits for pregnancy. This rise and fall in levels offers substantial evidence of therapeutic activity, but no bleeding occurred. The same absence of bleeding has been shown with estrogenic hormone[6] used for a similar purpose. One may speculate that any bleeding which may occur during pregnancy cannot be considered normal. The amounts of the different medications employed were physiologically comparable, but in the pregnant group the levels of pregnanediol were higher, which suggested more rapid and effective metabolism and excretion, and may be

related to the amount of estrogenic hormone. In the 3 nonpregnant patients the appearance of small amounts of pregnanediol prior to the beginning of therapy indicates that ovulation and corpus luteum formation had already occurred and amenorrhea may have been on the basis of delayed ovulation.

Summary

In patients with previously regular menstrual cycles, the use of progesterone-induced withdrawal bleeding, as a simple physiologic but nonspecific test for pregnancy or secondary amenorrhea, is highly accurate. In this series its accuracy was 100 per cent.

The oral or vaginal mode of administration is recommended over the intramuscular route, since by the oral and vaginal routes in 85 per cent of the patients the onset of the bleeding occurred between the third and the seventh days.

No alteration in the course of a gestation was noted with either standard dosage or excessively large dosage. No abortion can be attributed to the use of the progesterone.

In the cases of secondary amenorrhea the progesterone test was not only accurately diagnostic but therapeutic, since in 72 per cent of the nonpregnant patients the menstrual cycles were restored to normal regularity.

Grateful acknowledgment is made of the clinical supplies of progesterone provided by the following: Lutocylol (anhydrohydroxyprogesterone), supplied by Dr. C. H. Sullivan of Ciba Pharmaceutical Products, Inc., and Colprosterone (progesterone U.S.P.) supplied by Dr. J. B. Jewell of the Ayerst Laboratories.

References

1. Aschheim, S., and Zondek, B.: Klin. Wchnschr. **7**: 8, 1928.
2. Friedman, M. H.: Am. J. Physiol. **90**: 617, 1929.
3. Weisman, A. I., and Coates, C. W.: West. J. Surg. **52**: 121, 1944.
4. Galli-Mainini, C.: J. Clin. Endocrinol. **7**: 653, 1947.
5. Soskin, S., Wachtel, H., and Hechter, O.: J. A. M. A. **114**: 2090, 1940.
6. Garrett, S. S.: Am. J. Surg. **3**: 261, 1948.
7. Albright, F.: J. Maine M. A. **29**: 235, 1938.
8. De La Balze, F. A.: Semana méd. **1**: 953, 1948.
9. Kupperman, H. S., Blatt, M. H. G., Wiesbader, H., and Studdiford, W. E.: Obst. & Gynec. **1**: 550, 1953.
10. Soule, S. D.: Obst. & Gynec. **1**: 38, 1953.
11. Barfield, W. E., and Greenblatt, R. B.: Am. J. Obst. & Gynec. **64**: 1111, 1952.
12. Hady Gediz, M. A.: Türk. Ginek. Arsivi. **16**: 1827, 1951.
13. Hady Gediz, M. A.: Türk. Arch. Gynäk. **13**: 1575, 1947.
14. Caffier, P.: Zentralbl. Gynäk. **69**: 10, 1947.
15. Hayden, G. E.: Am. J. Obst. & Gynec. **69**: 931, 1955.

Discussion

DR. REGINALD A. SMITH, Rochester, Minn.—The evolution of the progesterone-induced withdrawal bleeding test for pregnancy has been well reviewed by Dr. Hayden. Noteworthy is the fact that all prior reports deal with only small series of cases. In the present paper, enough cases are studied to make significant the reported accuracy of 99 per cent. This accuracy is greater than that of the routine tests for pregnancy.

Dr. Hayden has said that this procedure is harmless and physiologic. This appears to be so when physiologic doses of progesterone are administered. When larger doses are given, however, the androgenic potential of progesterone must be considered. Lawson

Wilkins, Alvin B. Hayles, and Howard Jones recently discussed a few cases of hermaphroditism in children born after the administration of progesterone to the mother early in pregnancy. In these instances, large daily doses of progesterone, in conjunction with a yet unknown factor, apparently have exerted an androgenic effect on the genital development of the embryo. It is realized that progesterone is administered for various reasons early in pregnancy with great frequency and that few reports of hermaphroditism implicate progesterone as a possible cause. With the new high-potency preparations of progesterone and progesterone-like substances now available, this possible androgenic influence must not be forgotten.

It appears advisable, therefore, to continue the application of this useful test and, at the same time, to attempt to establish a physiologic minimal dose of progesterone that may be administered without impairing the accuracy of the test.

HIGH POTENCY PROGESTERONE DRUGS AND THREATENED ABORTION*†

C. Paul Hodgkinson, M.D., Eli J. Igna, M.D., and Alfred P. Bukeavich, M.D., Detroit, Mich.

(From the Department of Gynecology and Obstetrics, Henry Ford Hospital)

EFFORTS to arrest the process of spontaneous threatened abortion by the administration of either of two highly potent progestational agents were appraised in 61 patients. Sixteen were treated with 17-alpha-hydroxyprogesterone caproate‡ (hereafter identified as Drug A) and 45 with 17-alpha-ethinyl-19-nor-testosterone§ (Drug B).

Observed active uterine bleeding, graded from 1 plus to 4 plus, was used as the sole indication for initiation of therapy. The clinical scale used to adjudge the volume of uterine bleeding was as follows: 1 plus, equivalent to scant menstrual flow; 2 plus, equivalent to average menstrual flow; 3 plus, equivalent to heavy menstrual flow with small clots; and 4 plus, equivalent to heavy menstrual flow with passage of clots larger than 4 cm. in diameter.

Uterine cramps were an associated symptom in most of the patients; for the purpose of uniformity, however, uterine cramps when they occurred alone were not used as an indication for initiation of therapy. Also, a patient whose bleeding episode resembled that of implantation was eliminated from this study.

Treatment

Bed rest and mild barbital sedation served as adjuncts to therapy during the phase of bright red bleeding. Ambulation was permitted when the loss of bright red blood ceased, although this was frequently followed by a uterine discharge of black-brown mucoid material which continued in several patients until delivery.

Drug A.—Drug A was administered intramuscularly as follows:

250 mg. once each week‖	7 patients
125 mg. once each 2 weeks	1 patient
250 mg. immediately, then 125 mg. once each 2 weeks	1 patient
250 mg. once each 2 weeks	6 patients
250 mg. twice each week	1 patient

Drug A is highly active, with proved progestational action sustained for at least 10 days; the acme of pharmacologic response occurs about the seventh

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†Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

‡Delalutin, E. R. Squibb & Sons.

§Norlutin, Parke, Davis & Company.

‖Presently preferred schedule.

day and both the onset and loss of effect of the drug are gradual. After a single-dose injection in the estrogen-primed castrate, spotty progestational changes in the endometrium occur in 72 hours and fully developed changes in 96.[1, 2]

Drug B.—Drug B was administered orally according to the following schedule:

10 mg. each day	29 patients
20 mg. each day	4 patients
30 mg. each day	2 patients
30 mg. immediately, 20 mg. in 4 hours, 10 mg. in 4 hours, then 10 mg. each day*	10 patients

In contrast, the luteoid action of Drug B was prompt and the duration relatively brief. In the uniphasic, amenorrheic, estrogen-primed patient, the thermal response characteristic of progesterone was evident within 24 hours after the drug was administered and for 24 hours after it was stopped; withdrawal bleeding usually occurred 48 hours after the drug was discontinued. These changes were confirmed with the cervical mucus fern test (Fig. 1).

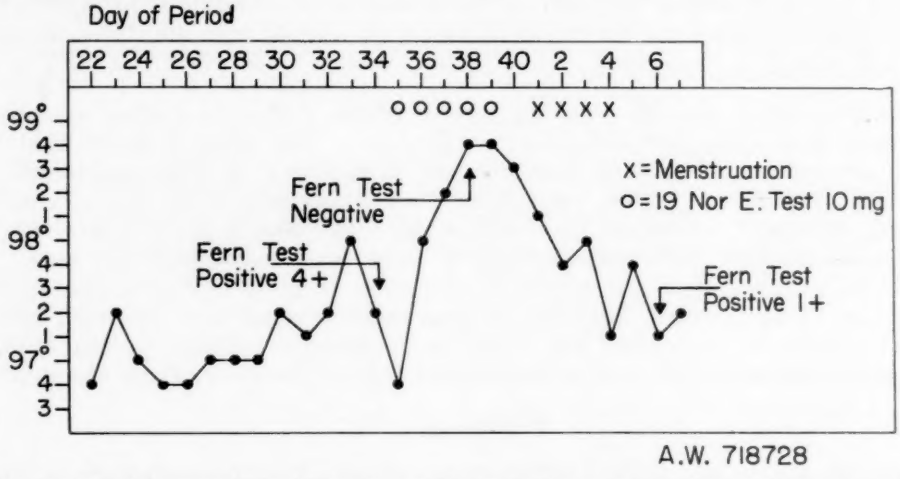

Fig. 1.—Basal temperature chart of an estrogen-primed amenorrheic patient given Norlutin, 10 mg. daily for 5 days.

Both drugs were equally well tolerated. Drug B was discontinued in one case upon the insistence of the patient's husband because he detected hoarseness which he ascribed to the effects of the drug. Although the symptom disappeared when the drug was stopped, the relevancy of the hoarseness to the effects of the drug was unconvincing and unproved. No other stigmas of masculinization were observed.

The duration of therapy ranged from a single dose to administration for 23 weeks. The largest amount of Drug A received by any one patient was 3,000 mg. over a 12 week period. Ten milligrams of Drug B was given daily to another patient for 23 weeks for a total dose of 1,610 mg.

Antecedent Pregnancy History

As indicated in Table I, prior to the present pregnancy the 61 patients had experienced 153 pregnancies; 36 had been delivered of 75 infants whose intrauterine age had reached at least the period of viability; 31 patients gave

*Presently preferred schedule.

a history of having had an aggregate of 78 abortions. Seven patients were habitual aborters by the rule of "3 consecutive spontaneous abortions" and 2 had had premature dilatation of the cervix. The poor obstetrical habits of these patients were emphasized by comparison of the patient-to-infant ratio of 1 to 2.2 to the patient-to-abortion ratio of 1 to 2.5.

TABLE I. PREGNANCY HISTORY

Antecedent Pregnancies.—	
No. or patients	61
No. of pregnancies	153
Infants Born.—	
No. of patients	36
Aggregate no. of infants	75 (49%)
Abortions.—	
No. of patients	31
Aggregate no. of abortions	78 (51%)

Results

The benefits from these drugs were evaluated according to their apparent influence upon: (1) the over-all pregnancy salvage, (2) the duration of pregnancy, and (3) the dynamics of abortion. Finally these results were compared with those obtained by bed rest and mild sedation in a control series of 297 patients.

TABLE II. PREGNANCY SALVAGE

DEGREE OF INITIAL BLEEDING	DRUG A		DRUG B		TOTAL
	ABORTIONS	PREGNANCY CONTINUED	ABORTIONS	PREGNANCY CONTINUED	
+	0	1	2	3	6
++	8	4	16	10	38
+++	0	0	7	3	10
++++	3	0	1	3	7
Total	11	5	26	19	61
% Salvage		31%		42.3%	39.4%

Pregnancy Salvage (Table II).—The over-all pregnancy salvage was 39.4 per cent. Although some difference was observed in the results obtained with Drug A as compared with Drug B, we were of the opinion that this difference was probably more apparent than real because it seems likely that both drugs are of nearly equal potency. Any advantage of Drug B was probably not due to a lessened comparative total pharmacologic effect of Drug A, but was rather inherent in the difference in the promptness with which the pharmacologic effect occurred.

Of the 61 pregnancies, 37 terminated in abortion and 22 in delivery of infants of a viable age. Two patients are in the eighth month of gestation. Including the 2 undelivered patients, the ratio of deliveries to abortions was 1 to 1.55.

Duration of Pregnancy (Table III).—Six infants weighed less than 2,500 grams at birth and were premature by pediatric standards, weighing 2,070, 2,110, 2,170, 2,296, 2,450, and 2,480 grams and being delivered at 34, 36, 38, 36, 36, and 36 weeks, respectively. The duration of gestation for the remainder was as follows: 40 weeks, 10; 38 weeks, 2; and 36 weeks, 2. A tendency to early delivery was noted in 40 per cent of the patients who received treatment with luteoid drugs.

TABLE III. DURATION OF GESTATION

	DRUG A		DRUG B	
	LIVE	DEAD	LIVE	DEAD
Term	4		10	
Premature	1		5	
Immature			1*	1
Undelivered			2	
Fetal anomalies	0	0	0	0

*Neonatal death (atelectasis).

There were strong indications that, once treatment was begun, the drug should be continued in the same or in increasing dosage until at least the thirty-eighth week of gestation. In one patient premature labor and delivery of a live, immature male occurred at 24 weeks, 2 weeks after Drug B had been decreased from 30 to 10 mg. daily.

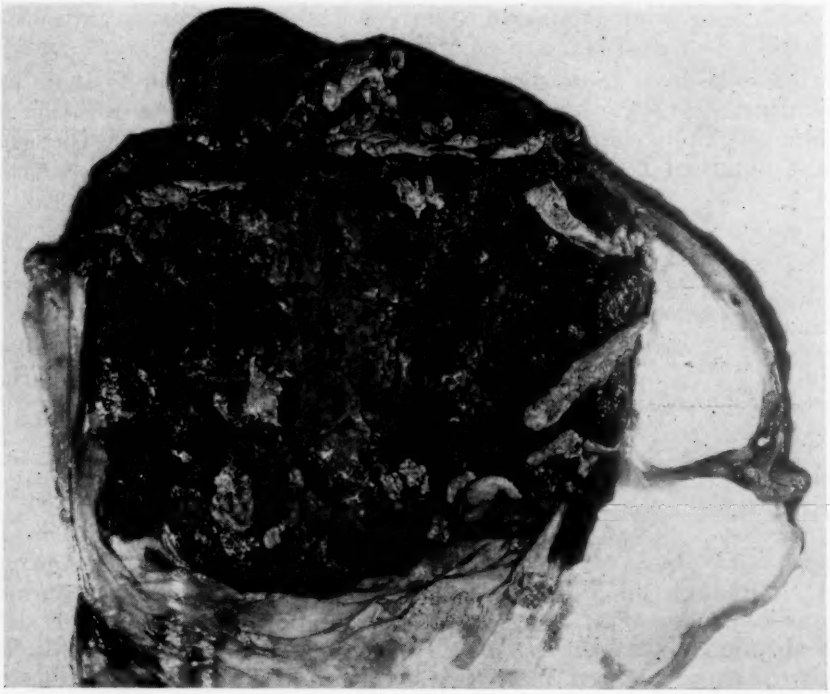

Fig. 2.—Placenta, maternal surface showing a large amount of amorphous fibrin.

The persistence of a black-brown mucoid discharge engendered a distinct feeling of insecurity. That the amount of discharge was correlated with the size of the retroplacental hemorrhage was observed in one patient who had been under treatment with Drug B from 10 weeks' gestation and who was delivered at 36 weeks of a 2,470 gram male infant. The large amount of retroplacental amorphous fibrin is shown in Fig. 2.

Dynamics of Abortion (Table IV).—Twenty of the 37 abortions were immediate. In 17 cases abortion was delayed: the bright red bleeding ceased, uterine contractions subsided, and the cervix remained closed. These circumstances prevailed for variable periods of time and eventually terminated in spontaneous abortion, except for 2 cases. One of these patients who received Drug B, 10 mg. daily for 10 weeks, failed to abort for 32 weeks. Although the

uterus regressed to nearly normal size, viable placental tissue was obtained by curettement, and spontaneous menstruation recommenced 8 weeks later. Another patient failed to menstruate for 20 weeks after 12 weeks of treatment with Drug A, 250 mg. twice weekly. Placental tissue was removed by curettement and menstruation followed 6 weeks later.

Eight patients developed the syndrome of missed abortion, in that they retained a nonviable conceptus for 8 weeks or longer. One patient developed a hydatidiform mole.

TABLE IV. DYNAMICS OF ABORTION

	DRUG A	DRUG B	TOTAL
Total number aborted	11	26	37
Immediate abortion	6 (54.5%)	14 (53.8%)	20 (54%)
Delayed abortion:			
4 weeks	1	8	
8 weeks	2	3	
12 weeks	1	0	
20 weeks	1	0	
32 weeks	0	1	
Total	5 (45.5%)	12 (46.2%)	17 (46%)

Control Group.—These results were compared with similar observations by one of us (C. P. H.) of a control series treated by bed rest and mild sedation. The original purpose of the control series was to provide a comparison with results of barbital and morphine sedation. The differences were so slight that the results were never published; the records were combined to make a control series of 297 patients. Because the qualification, active uterine bleeding, was the symptom common to both groups, suitable comparisons are possible with minimal distortion from subjective influences.

TABLE V. CONTROL VERSUS LUTEOID-TREATED PATIENTS

	CONTROL	LUTEOID TREATED
Number	297	61
Discharged pregnant	15.5%	39.4%
Aborted within 2 weeks	81.2%	32.6%
Aborted after 2 weeks	3.3%	28.0%

Comparative Pregnancy Salvage (Table V).—The pregnancy salvage under the bed rest-sedation program of the control group was 15.5 per cent (46 patients); spontaneous abortion occurred in 84.5 per cent. In the luteoid-treated group 39.4 per cent of the pregnancies continued.

Although 60.6 per cent of the patients aborted when under luteoid therapy and 84.5 per cent under the bed rest-sedation program of the control series, certain differences in the procedure of abortion were evident. In the control group, 81.2 per cent of the patients aborted within 2 weeks of the onset of symptoms. Appreciable delay in the time of the abortion was observed in the luteoid-treated group: 32.6 per cent of the patients aborted within 2 weeks of the time of onset of uterine bleeding and 28 per cent after 2 weeks.

Pathologic Ova (Table VI).—An effort was made in the control series to classify abortuses according to the grouping suggested by Mall and Meyer.[3] Examination was restricted to abortuses expelled intact within the amniotic sac; suitable specimens were obtained from 83 patients. Pathologic abortuses

were observed in 68.7 per cent and normal specimens in 31.3 per cent of the material studied. Five hydatidiform moles and one chorioadenoma destruens were observed.

TABLE VI. CLASSIFICATION OF PATHOLOGIC OVA

	CONTROL	LUTEOID TREATED
Number studied	83	
Normal conceptus	31.3%	Not done
Pathologic conceptus*	68.7%	Not done
Hydatidiform mole	1.68%	1.55%
Chorioadenoma destruens	.33%	None

*According to classification of Mall and Meyer.

Salvage Potential (Table VII).—It is difficult by correlation of published reports to evaluate the efficiency of therapy for threatened abortion. Varied and mixed standards have been used by different authors and the results frequently seem to depend as much upon subjective enthusiasm as upon objective findings.

In the present study, an effort was made to gain some insight into the potential salvage for the patient with threatened abortion when the major symptom was uterine bleeding. From the experience of the control group, the potential salvage was adduced by adding the percentage of patients still pregnant when discharged to the percentage of normal abortuses: 15.5 per cent plus 31.3 per cent, respectively, or 46.8 per cent. Hertig[4] using similar methods estimated the salvage potential for threatened abortion to be about 60 per cent.

From this syllogistic calculation, the efficiency of the bed rest-sedation and luteoid drug therapy programs could be compared. Using the potential salvage percentage of 46.8, the theoretical number of pregnancies which might have been saved from the 297 patients in the control group was 138. With only 46 salvaged, the efficiency of the bed rest-sedation program approximated (46/138) 33.2 per cent.

In the luteoid-treated series, 39.4 per cent, or 24 patients, recovered from uterine bleeding and carried their pregnancies beyond the age of viability. The number of potentially salvageable pregnancies, using percentage of 46.8 arrived at above, averaged between 28 and 29, making the efficiency of luteoid therapy for this group of patients (24/28.5) 84 per cent.

TABLE VII. POTENTIAL PREGNANCY SALVAGE

	CONTROL	LUTEOID TREATED
Discharged pregnant	15.5%	39.4%
Normal conceptuses	31.3%	
Salvage potential, maximum	46.8%	
Efficiency of luteoid therapy		84%

Comment

As progestogens, Drug A (17-alpha-hydroxyprogesterone caproate), Drug B (17-alpha-ethinyl-19-nor-testosterone), and progesterone share many physiologic similarities. In common, they inhibit ovulation, prolong the menstrual cycle, serve as thermogenic agents, and evoke characteristic changes in the vaginal epithelium and cervical mucus. Unlike progesterone, neither Drug A[5] nor Drug B[6] stimulates an augmented excretion of pregnandiol. While Drug

A and progesterone cause secretory changes of striking similarity in the endometrium,[2] Drug B causes a disproportionate change characterized by decidua-like changes in the cells of the stroma and the epithelium and arrest of the glands in the late proliferative phase.[7]

Experimental studies have disclosed other differences. Progesterone, in rats, causes a reduction in the size of the litter from an average of 11 to less than 3 and a high percentage of abortions[8]; in prepubertal mice stimulated to copulate by the administration of gonadotropin, it permits implantation of fertilized ova and delivery of viable young[9]; in cattle, breeding efficiency is increased,[10] and in human males,[11] it induces azoospermia. Drug A, used under similar circumstances, does not cause a reduction in litter size or abortion in rats[8]; it will stimulate implantation in prepubertal mice but will not sustain pregnancy,[9] although it does increase breeding efficiency in cattle[10] and azoospermia in human males.[11]

Drug A is neither estrogenic nor androgenic,[12] nor is it effective when administered orally. Drug B has negligible androgenic and mild estrogenic activities, and it is effective when administered either orally or parenterally.[13] Drug B is anabolic rather than catabolic and it causes salt retention rather than salt elimination. It is not known whether the estrogenic activity of Drug B is caused by contamination with ethinyl-estradiol-3-methyl ether or whether this property is inherent in the chemical formula of the drug.

While the similarities in pharmacologic action far outweigh the dissimilarities, and "progestational" is the proper term for these new agents, in the appraisal of their clinical value it is necessary that these differences be kept in mind. In obstetric patients who experience uterine bleeding of sufficient degree to justify the diagnosis of threatened abortion, the most important salutary attributes of luteoid action appear to be those associated with the metabolic influence of progesterone upon endometrium and the inhibition of myometrial contraction.

The speed of action also must be considered. Myometrium differs from other muscles by the extreme slowness of its reactions and its sensitivity to ovarian steroids.[14] Also, dominance of control probably rests within the myometrial fibers per se rather than in a central nerve center, and the initiation of kinetic function is physiochemical rather than neurogenic. It has been shown that the degree of myometrial excitation depends upon the establishment of electrochemical gradients which probably occur as the result of a shifting of intra- and extracellular ions. Estrogen increases the electrochemical gradients and is the activator of myometrial excitation; progesterone abolishes the gradients and is the inhibitor. The ability of progesterone to inhibit the actions of oxytocin, histamine, epinephrine, and acetylcholine has been explained on this basis.

Neither estrogens nor progesterone are active upon direct contact. Denervated whole uteri respond to the motility-stimulating action of estrogen and to the motility-inhibiting action of progesterone in wholly typical manners.[15] Because the initiation of kinetic function is physiochemical rather than neurogenic, latent periods of variable duration occur between the time of administration and the time of pharmacologic action of estrogenic and progestational drugs. The average times for the drugs in question are: progesterone, 12 to 24; Drug A, 48 to 72; and Drug B, 12 to 24 hours. For accurate appraisal of the pharmacologic action of steroid drugs of these types, it is essential that potentialities and limitations of action be established as standards of reference.

In the present study, 20 patients had abortions within a few hours after initiation of luteoid therapy, and it was apparent that the drug had no influence upon the dynamics of abortion in these patients. In 17 patients abortion was

delayed. It appeared likely that the course to be followed by any patient when first observed depended upon how far the abortion had advanced before treatment was initiated and upon the viability of the conceptus. If the state of abortion had advanced to the point where it could not be inhibited during a latent interval of at least 12 hours, immediate abortion was probable. If, on the other hand, the state of abortion was less advanced and progress less rapid, so that the latent period of the action of the drug could be safely tolerated, the abortion was likely to be delayed for a variable period of time. In one patient the delay extended for 32 weeks. The eventual state of the pregnancy depended upon the viability of the conceptus: if alive, the pregnancy was likely to continue; if dead, abortion eventually occurred.

Conclusions

1. In threatened abortion characterized by active uterine bleeding, a comparative appraisal was made of the influence of two high-potency progestational agents upon: (1) total pregnancy salvage, (2) duration of gestation, and (3) dynamics of abortion.

2. In the luteoid-treated group the pregnancy salvage was 39.4 per cent; a tendency to early delivery was noted in 40 per cent of the patients; and the dynamics of abortion were delayed for 4 weeks or longer in 46 per cent of patients who aborted.

3. These results were contrasted with those in a control group of 297 patients evaluated by similar standards in which the pregnancy salvage was 15.5 per cent and the delayed abortion rate 3.36 per cent.

4. The potential pregnancy salvage for obstetrical patients who have active beeding during early pregnancy was adduced to be 46.8 per cent. On this basis 84 per cent of the salvageable pregnancies were preserved by the luteoid agents.

For making available Delalutin, we are gratefully indebted to Dr. Edward C. Reifenstein, Jr., and the E. R. Squibb & Sons Company; and for Norlutin to Dr. John Mote, the Chemical Specialties Company, New York, N. Y., Syntex, S. A., Mexico City, D. F., Mexico, Parke, Davis & Company, Detroit, Mich.

Addendum.—Lawson Wilkins and Howard W. Jones, Jr.,[16] recently published a clinical note on iatrogenic origin of secondary sex characteristics as a result of administration of norethynodrel to pregnant women during the fourth to the eighth week of gestation for the treatment of threatened abortion. An appraisal has been made of infants born to patients in the present study as follows: female infants, 11; male infants, 11. No gross abnormality was detected by either the obstetrician or the pediatrician in charge of the nursery. All male infants were circumcised prior to discharge, except two prematures. No female infant displayed an enlarged clitoris.

References

1. Thomas, H. H.: Repart to Squibb Institute for Medical Research, June 28, 1955.
2. Davis, M. E., and Wied, G. L.: J. Clin. Endocrinol. **15**: 923, 1955.
3. Mall, F. P., and Meyer, A. W.: Contrib. Embryol. **12**: 364, 1921.
4. Hertig, A. T., and Livingstone, R. G.: New England J. Med. **230**: 797, 1944.
5. Langecker, H.: Arch. exper. Path. u. Pharmacol. **225**: 309, 1955.
6. Pincus, G., Rock, J., and Garcia, C. R.: Ann. New York Acad. Sc. (In Press.)
7. Epstein, Jeanne A., and Kupperman, H. S.: Ann. New York Acad. Sc. (In press.)
8. Velardo, J. T.: Ann. New York Acad. Sc. (In press.)
9. Smithberg, M.: Ann. New York Acad. Sc. (In press.)

10. Gassner, F. X., Johnson, K. R., Nalbandov, A. V., and Reifenstein, E. E., Jr.: Ann. New York Acad. Sc. (In press.)
11. Heller, C. G., Laidlaw, W. M., and Nelson, W. O.: Ann. New York Acad. Sc. (In press.)
12. Kessler, W. B., and Borman, A.: Ann. New York Acad. Sc. (In press.)
13. McGinty, D. A., and Djerassi, C.: Ann. New York Acad. Sc. (In press.)
14. Csapo, A. I.: The Molecular Basis of Myometrial Function and Its Disorders. In Congrès international de gynécologie et d'obstétrique, La Prophylaxie en gynécologie et obstetrique, Geneva, 1954, Librairie de l'Université, Georg & Cie S. A., pp. 693-702.
15. Reynolds, S. R. M.: Physiology of the Uterus, ed. 2, New York, 1949, Paul B. Hoeber, Inc., pp. 483.
16. Wilkins, Lawson, and Jones, Howard W.: Obst. & Gynec. 11: 355, 1958.

Discussion

DR. RUDY F. VOGT, Louisville, Ky.—In Louisville, I see almost daily our 20 Board Members who practice obstetrics and, with one or two minor exceptions, their treatment of threatened abortion goes little beyond limiting the patient's activities and sedation. Some volunteer that they use token doses of stilbestrol and some large doses of the various forms of ascorbic acid.

The high percentage of abnormal tissue found in abortion specimens has been reviewed by many, besides the detailed work of Dr. Hertig. Last year, Drs. Huber and Melin in Indianapolis reported that 76 per cent of their specimens showed abnormal fetuses, and over 50 per cent of these molar changes. Certainly most of us frequently see gross abnormalities in the specimens we have a chance to observe, and know how many are lost to inspection.

A few years ago some work was reported from Louisville, in which a standard daily dose of estrogen plus large doses of progesterone were able to produce and maintain a decidual reaction in normal women. The work of Drs. Bradbury and Long was carried on by Dr. William Durham in a unique institutional setup where weekly endometrial biopsies were obtained. They found that stilbestrol, 1 mg. daily, and progesterone, 250 to 375 mg., were needed to develop the decidua. Until fairly recently it was not practical to give such a dosage. Now, with preparations that have a strength of 125 mg. per cubic centimeter, doses of 250 mg. per week are practical and easy to administer.

Dr. Hodgkinson has increased his salvage rate from 15.5 to over 39 per cent. There probably will be times when all of us will give his plan a try. However, some threatened abortions will quiet down with mere bed rest and missed abortions are distressing to patients.

CARDIOVASCULAR REACTIONS TO PITOCIN*

James R. Reinberger, M.D., and
William F. Mackey, M.D., Memphis, Tenn.

(From the Obstetric Department, Methodist Hospital)

THE parenteral administration of posterior pituitary extracts for prevention or control of postpartum hemorrhage has been a routine procedure for almost half a century. This practice has been so successful that one now hesitates to leave the newly postpartum patient until one of the posterior pituitary extracts has been given. And yet this administration is not without danger.

Reactions of unusual character vary from mild to severe, and sometimes fatal. Many mild reactions go unrecognized, and even severe ones are overshadowed by, or more often are attributed to, the operative procedure, blood loss, or the anesthetic. These reactions may result from a peculiar sensitivity to the drug or other component elements of the posterior pituitary gland solution. The manufacturers of posterior pituitary extract realize this fact, and have subsequently divided the extract of posterior lobe into more refined elements. They have separated a pressor element called Pitressin, and an oxytocic element, called Pitocin. They have also found that, regardless of the technique used in separating these elements, a small amount of each factor is present in each refined preparation. The U. S. Pharmacopeia permits such an assay at the present time. It is for this reason that the extract of the whole posterior pituitary lobe should not be used when a specific reaction is desired, especially in obstetrics where only the oxytocic element is desired. Pitocin is the drug of choice,[9, 11] but even our use of Pitocin for induction of labor and control of postpartum hemorrhage has produced both mild and severe reactions. Pitocin reactions may be due to unusual sensitivity of the patient, to synergistic action with the anesthetic agent, and even to improper preparation and assay. These latter were reported in 1953 with certain lots of Pitocin having 18 pressor units per cubic centimeter rather than ½ unit or less.[3] These lots of Pitocin were recalled by the drug house but it is possible that the severe reactions which we report here could have been due to the pressor factor rather than the oxytocic element. Recently, a synthetic Pitocin† has been made available which is said to be absolutely free of the pressor factor.[1, 2, 8]

*Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

†Syntocinon, Sandoz Pharmaceuticals.

Pharmacology of Pitocin.[10]—The effect of Pitocin on blood pressure is variable; occasionally, there is a rise. It increases cardiac output. Its effect on the coronary arteries is theoretically nil, but actually they are constricted. The electrocardiogram is said by many authors not to be affected, but our case indicates that this may not always be true. The peripheral circulation is theoretically not affected, but actually shock has been reported. There is no change in metabolism. Contraction of the pregnant uterus is immediate and intense.

Cyclopropane gas is a parasympathetic stimulant. It causes bronchial constriction which may precipitate an asthamtic attack in the susceptible patient. It also tends to produce cardiac arrhythmias with displacements of the rhythm centers. The range is bradycardia to ventricular fibrillation. The combination of two parasympathetic stimulants, cyclopropane and pituitary extract, is most dangerous.[11] In the circulatory system, they have a synergistic tendency to produce hypertension and cardiac arrhythmias. It is important, therefore, never to use posterior pituitary extract when an oxytocic is indicated in a patient under cyclopropane anesthesia.

A survey of hospitals reveals that more attention should be directed to the type of posterior pituitary extract being used in the departments of obstetrics. The department of obstetrics should not have any surgical Pituitrin for this preparation should never be used as an oxytocic. The department of surgical gynecology should have both obstetrical and surgical Pituitrin and, if prescribed, the type of Pituitrin should be specifically ordered; otherwise, surgical Pituitrin could be given.

Case Report

Past History.—Appendectomy was performed in 1944. Right oophorectomy and lysis of pelvic adhesions were performed in 1949. A cesarean section was performed July 4, 1952, because of primary inertia.

Hospital Course.—The patient was admitted to Methodist Hospital in November, 1954, at 38 weeks' gestation for elective cesarean section. The blood pressure was 112/70; hematocrit, 44; and urinalysis, negative. A spinal anesthetic was given by a doctor-anesthetist. An incision was made, removing the old scar. Omental adhesions had to be released before the pregnant uterus could be exposed. The uterus was then opened and a normal male infant was extracted. The infant weighed 6 pounds, 9 ounces, and cried immediately. The placenta and membranes were removed. Pitocin, 1 c.c., was then injected into the uterine muscle. The patient, who had been perfectly calm and composed, then complained immediately of severe pain in the chest, associated with shortness of breath. This reaction was associated with a rapidly rising pulse rate from 85 to 120 per minute. This pulse elevation lasted about 30 minutes. At the time the procedure was finished (1 to 1½ hours), the pulse was 95 per minute, blood pressure 90/60. The patient was sent to her room awake, talking, and in excellent condition.

Postoperative Course.—An electrocardiogram was ordered 3 hours after operation This was ordered for two reasons: first, because of the unusual reaction of this patient after injection of Pitocin into the uterus and, second, because several months previously an unusually severe similar reaction had occurred in another patient but, unfortunately, no electrocardiogram was obtained. The electrocardiogram was interpreted by Dr. J. B. Witherington as an abnormal tracing showing coronary spasm, probably due to the administration of Pitocin into the uterus at the time of cesarean section. The first postoperative days were stormy, with oxygen necessary for dyspnea, and Wangensteen suction for distention. Blood transfusions and general supportive measures were given. During these 3 days the pulse would rise to 150 per minute at times and would skip every third beat. By the third postoperative day, however, a repeat electrocardiogram showed

"a normal tracing; the abnormalities previously present may have been due to coronary insufficiency or acute pulmonary embolism," as interpreted by Dr. Warren Kyle. The blood pressure was 110/70 and pulse 80 on the third postoperative day. From then on, recovery was rapid and the patient was discharged home on the tenth postoperative day.

Follow-Up Examinations.—For the first 2 years there were no significant findings except that at times the patient's pulse would drop to 30 or 40 per minute. These attacks were associated with some distress and weakness. At the last visit, 3 years postoperatively, in October, 1957, there were no complaints or abnormalities.

Comment

We have now discontinued the use of Pitocin or any drug in the uterus at the time of cesarean section. Since we are not injecting any drug into the uterus, we have found that we really do not need any oxytocics in most cases. If an oxytocic is needed, it can be given intramuscularly by the anesthetist. Intravenous Pitocin after normal delivery has just lately been shown to cause a more frequent and higher rise in blood pressure than either Ergotrate or Methergine.[4] This is very important, especially since it implies that Pitocin is dangerous in toxemia.[12]

We do not completely agree with the statement of Dr. Eastman[5] in the eleventh edition of his textbook: "It is probable that intramuscular Pitocin has no place in the first or second stages of labor in modern obstetrics." We do, however, heartily agree with his words of caution as to the use of an intravenous drip of Pitocin. He contends that intravenous-drip Pitocin is safer than its intramuscular use; yet, to our knowledge, in Memphis, 3 cesarean sections have been done recently because of tetanic uteri and fetal distress following Pitocin infusions. Also, 3 ruptures of the uterus have occurred in Memphis, caused by the use of intravenous-drip Pitocin. Other tragic accidents, even death, have been reported elsewhere.[6] We cannot recall such cases following intramuscular Pitocin, even in 1 c.c. doses.

Summary

A case of coronary constriction during a cesarean section under spinal anesthesia has been reported. It is believed that this complication was due to the injection of Pitocin into the uterus.

References

1. Dieckmann, W. J., and Fugo, N. W.: Exhibit, Federation of American Societies for Experimental Biology, Chicago, April, 1957.
2. Bishop, E. N.: To be published.
3. Jackson, R. L.: Personal communication.
4. McGinty, L. B.: West. J. Surg. **64**: 22, 1956.
5. Eastman, N. J.: Williams Obstetrics, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc., p. 831.
6. Barno, Alex, Freeman, D. W., and Belleville, T. P.: Obst. & Gynec. **9**: 336, 1957.
7. Passloe, C. P., Morris, L. B., and Orth, Sidney O.: Anesthesiology **11**: 76, 1950.
8. Boissonnas, R. N., Guttmann, S., Juguerowd, P. H., and Waller, J. P.: Helvet. chem. acta **38**: 491, 1955.
9. Hellman, L. M., Kohl, S. G., and Schechter, N. R.: Am. J. Obst. & Gynec. **73**: 507, 1957.
10. Pharmacopeia of the United States, Fifteenth Revision, 1955, p. 494.
11. Belinkoff, Stanton: Am. J. Obst. & Gynec. **44**: 109, 1944.
12. Jackson, R. L., and Decker, D. G.: Proc. Staff Meet., Mayo Clin. **28**: 20, 1953.

Discussion

DR. J. L. JACKSON, III, Wichita Falls, Texas.—Many reports attest the danger of the combined use of cyclopropane anesthesia and pituitary extracts. However, the type of shock described by Dr. Mackey following the administration of Pitocin is, perhaps, not so well recognized.

After I discussed the contents of Dr. Mackey's paper with my colleagues in Wichita Falls, Dr. Richard Bates recalled a similar case which occurred at Southwestern Medical Center, in Dallas, Texas, during his residency. While Dr. Bates was performing a cesarean section, 1 c.c. of pituitary extract was injected into the uterine muscle. Within a few moments, the patient went into profound shock and failed to respond to the usual forms of therapy. Later she received digitalis and it was only then that she began to respond. It was approximately 48 hours before she was considered out of danger.

After a review of almost 12,000 deliveries at the Wichita General Hospital, Wichita Falls, Texas, since 1949, only one case was found which could possibly be called Pitocin shock. Mrs. M. W., aged 23, para ii, gravida iii, was delivered of a 9 pound, 1 ounce, stillborn fetus after a moderately difficult midforceps delivery. A few minutes following the supposed administration of intravenous Ergotrate and intramuscular Pitocin, the patient went into profound shock. She failed to respond to the administration of Coramine, oxygen, and intravenous fluids. Only after digitoxin did she begin to respond. It was 24 hours before she was considered out of serious danger. No cause for this incident was apparent at the time.

Dr. Bates also recalled 3 additional cases at Southwestern Medical School which were designated as Pitocin shock. These cases presented a picture similar to that of Dr. Mackey's case except that the shock occurred following a vaginal delivery. In every case, 1 c.c. of Pitocin was accidentally administered intravenously. These 3 patients presented a similar shocklike syndrome which responded following the administration of some digitalis preparation. Combining the information obtained from these 5 cases, and Dr. Mackey's case, it appears that this syndrome of Pitocin shock occurs following the accidental administration of a whole cubic centimeter of Pitocin intravenously. It is my opinion that in both Dr. Mackey's case and in Dr. Bates's cesarean section, the pituitary extract was inadvertently administered intravenously rather than into the uterine musculature. In Dr. Bates's other 3 cases accidental administration of 1 c.c. of Pitocin intravenously was definitely considered to be the cause of the shock syndrome.

In the case reported from the Wichita General Hospital I would like to surmise that the patient received Pitocin intravenously and ergot intramuscularly, for this type of accident would precipitate the shock syndrome that this patient showed.

To add emphasis to the belief that shock follows the accidental administration of large doses of Pitocin intravenously, in the 12,000 cases reviewed at the Wichita General Hospital it was discovered that 75 per cent of the patients received Pitocin in one form or another. Among the cases reviewed, there was no suggestion of shock following the administration of Pitocin in small doses intravenously or large doses intramuscularly.

AN EVALUATION OF CARCINOMA OF THE CERVIX ASSOCIATED WITH PREGNANCY*

JOHN H. HOLZAEPFEL, M.D., AND HARRY E. EZELL, JR., M.D.,
COLUMBUS, OHIO

(From the Department of Obstetrics and Gynecology, College of Medicine, Ohio State University)

THE treatment of carcinoma of the cervix presents many difficulties, but when the problem is complicated by the presence of a fetus, the difficulties are magnified many times.

The treatment of carcinoma of the cervix with associated pregnancy usually leaves the physician with a deep sense of dissatisfaction. Part of this stems from the unanswered question whether pregnancy influences the progression of carcinoma of the cervix. There is considerable difference of opinion among the various authors who have reviewed the subject. When we consider how few cases one individual sees in a lifetime it is clear that authority on the subject from personal experience is impossible to achieve. In such a situation a review article has particular merit.

Material

The material for this study has been obtained from the Gynecologic Tumor Clinic, Department of Obstetrics and Gynecology, College of Medicine, Ohio State University Health Center.

Twenty-eight patients with carcinoma of the cervix associated with pregnancy were found in the total tumor registry of 1,332 patients from the years 1940 to 1957. As can be seen by reference to Table I, the majority of patients have registered since 1950.

TABLE I. NUMBER OF CASES BY YEAR OF REGISTRATION

1940-1949		8
1950-1957		20
	1950	1
	1952	3
	1953	2
	1955	6
	1956	4
	1957	4
Total tumor registration		1,332

This table should not be interpreted as indicating a general increase in the incidence of carcinoma of the cervix associated with pregnancy. The annual

*Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

total admissions to the Tumor Clinic have also increased steadily since 1950. One would like to attribute part of the increase to the intensity of cancer education of medical students, physicians in practice, and the lay public. Credit may also be given to the more general use of cytologic diagnostic techniques.

TABLE II. DISTRIBUTION OF NEW CASES BY STAGES

STAGE	NO. OF CASES	%
0	1	3.6
I	15	53.6
II	8	28.6
III	4	14.2
IV	0	0.0
Total	28	100.0

It will be quickly seen from Table II that the majority of the patients studied had a Stage I lesion. It should be noted that 3 of these 15 patients changed their stage so rapidly that the correctness of their original staging is questioned. One patient died 2 months after admission. The second patient changed from Stage I to Stage IV within 15 months and the third changed from Stage I to Stage IV within 8 months.

Incidence

The reported incidence of carcinoma of the cervix associated with pregnancy varies among different clinics. This is neither surprising nor is it of extreme practical importance. The average incidence is accepted as 0.05 per cent or 1 per 2,000 obstetric patients. Of 925 patients with carcinoma of the cervix registered in the Gynecologic Tumor Clinic from 1940 to 1957 there were 28 patients with an associated pregnancy; this represents an incidence of 3.0 per cent in our own clinic. This figure is higher than that generally reported, but the Ohio State University Health Center serves a rather large geographic referring area of central Ohio. The important point to remember regarding incidence is that the combination of the two conditions is not rare and anyone entrusted with the care of the female patient should maintain a "high degree of suspicion."

Age.—Our figures confirm the findings of Kistner and associates[5] and others in that the age incidence of patients with carcinoma of the cervix associated with pregnancy is lower than that of nonpregnant patients with carcinoma of the cervix. The oldest patient was 43 and the youngest patient was 25. The average age was 32 years. It should be noted that the greatest number of patients were found in the 30 to 40 age group, as seen in Table III. It should also be noted that 24 patients were white while 4 were Negroes.

TABLE III. AGE INCIDENCE

AGE GROUP	NO. OF CASES
20-30	7
30-40	19
40-50	2

Parity.—Macklin[7] has reported that cervical carcinoma occurs with undue frequency among married women who have begun their childbearing at an early age. In her study, patients with cervical carcinoma gave histories of an average of three pregnancies before the women with no cervical cancer had their first pregnancies. The most striking point of difference between these patients and the women without cervical carcinoma is the age at which they began

their pregnancies. This indicates that parity is not as important a factor as early childbearing. It is our experience also that the majority of patients were multiparas with large families. The exact ages at which childbearing had begun are not available for the group. There were only 4 primiparas.

Symptoms.—Abnormal bleeding is the most common symptom in carcinoma of the cervix associated with pregnancy. The bleeding may be initiated by trauma to the cervix or may be entirely spontaneous. It may occur during any trimester of pregnancy or occasionally may appear as persistent postpartum bleeding. There were 4 instances of postcoital bleeding or spotting, 13 other instances of bleeding during pregnancy, and 2 instances of persistent postpartum bleeding lasting beyond 6 weeks. Since several of the patients had multiple symptoms, the number of recorded symptoms does not correspond exactly with the total number of patients in the series.

In 7 cases the suspicious appearance of the cervix suggested the diagnosis of carcinoma of the cervix. There were several patients in whom bleeding during pregnancy plus a suspicious appearance of the cervix suggested the diagnosis of carcinoma of the cervix.

Four patients were without any symptoms whatsoever and the diagnosis was made from routine cytology slides in the prenatal clinic. All of the positive slides were confirmed by either biopsy or cold conization of the cervix or both. All of the histologic sections from these 4 patients revealed invasive carcinoma.

Finally, in one case, both the carcinoma of the cervix and the pregnancy were discovered by accident in a uterus removed by vaginal hysterectomy for uterine prolapse. This patient was referred to the Gynecologic Tumor Clinic by a surgeon after the unfortunate accident was discovered.

Diagnosis

There is unanimity of opinion that prognosis in carcinoma of the cervix is primarily dependent upon the clinical stage of the disease. Many authors, Kottmeier,[6] Kistner,[5] and Sadugor,[13] have shown that the trimester of the pregnancy in which the diagnosis of carcinoma is made also influences the prognosis of the disease. Therefore, early diagnosis and treatment are all important for favorable prognosis. Early diagnosis may be more easily accomplished if the program outlined by Montgomery[10] in 1954 is followed:

1. At the onset of pregnancy, inspection of the vagina and cervix by speculum should supplement the bimanual examination.
2. Cytologic examination of all patients is recommended.
3. Lesions of the cervix that bleed or present a suspicious appearance must be subjected to biopsy.
4. Spotting or bleeding during pregnancy calls for repetition of cervical inspection and for cytologic examination and biopsy.
5. Vaginal and cervical inspection are to be repeated 6 to 8 weeks before term.
6. Before an erosion is treated post partum, cytologic examination or biopsy must be done.

To this outline should be added cytologic examination and biopsy of the cervix when abnormal postpartum bleeding occurs.

It cannot be emphasized too strongly that a careful pelvic examination, both bimanual and speculum, during pregnancy for investigation of abnormal

bleeding has never been proved to cause complications. There is ample proof that single and multiple cervical biopsies may be done safely during pregnancy with proper precautions and conditions. A cold-knife conization may also be done, although one would certainly not suggest indiscriminate use of this procedure.

The routine use of the Papanicolaou smear at the time of the initial pelvic examination is to be recommended. It should be clearly understood however, that cytologic tests alone should not be relied upon either to refute or to confirm the diagnosis of carcinoma of the cervix. Any suspicious or positive cytologic results should lead to further diagnostic tests for histologic evaluation.

Treatment

The general policy of the Gynecologic Tumor Clinic has always been preference for irradiation over surgery. Of the 28 patients, 22 were treated by irradiation alone, 5 by a combination of irradiation plus radical surgery, and one patient (carcinoma in situ) received no treatment during her pregnancy. Four of the 5 patients treated by radical surgery were treated in the early 1940's and of these 4 patients, 3 are still alive. The radical surgery did not include pelvic lymphadenectomy. The fifth patient received irradiation primarily and radical surgery was resorted to as treatment for a central recurrence of the carcinoma.

A suggested program for therapy by trimester is outlined below:

First Trimester.—Therapy is initiated with deep external x-ray, with 3,000-3,500 r delivered to the midpelvic plane over a 3 week period. Spontaneous abortion will usually occur during this phase or shortly thereafter; however, if it does not, curettage is recommended rather than to wait or to use central therapy while the patient is still pregnant. Central therapy is accomplished by the use of either cobalt or radium, with 7,000 r delivered to point A. It is suggested that central therapy be divided into two phases with the second application delayed 7 to 10 days after the first application.

Occasionally a large, friable, fungating lesion of the cervix may be encountered, and in such a situation, certainly, a hysterotomy is preferable to abortion or curettage, particularly if the patient is late in the first trimester. If the diagnosis is made at the time of spontaneous abortion, which occurred in 4 of the 28 cases, then central therapy should precede external therapy.

As an alternative in Stage I patients, a radical hysterectomy plus bilateral pelvic lymphadenectomy may be considered. As yet there has not been sufficient personal experience nor has the literature provided sufficient reports to indicate that radical surgery is superior to irradiation therapy.

Second Trimester.—Here, first consideration is given to emptying the uterus by hysterotomy. External x-ray (3,000 r) should be started on the seventh to the tenth postoperative day, with care to protect the abdominal incision by a lead strip. Following completion of external therapy, central therapy is given. This is accomplished with cobalt or radium, with 7,000 r delivered to point A. If external therapy is given while the uterus is involuting, no time is lost. To administer central therapy while the patient is still pregnant seems contrary to basic principles.

An alternative during this trimester also is a radical hysterectomy and bilateral pelvic lymphadenectomy. One of our patients recently had this form of therapy. This patient is not included in the study, however, because her therapy is too recent to be fully evaluated.

Third Trimester.—During the third trimester, first consideration should be given to a viable or nearly viable fetus. Here one must individualize therapy in accordance with the duration of the pregnancy. If the diagnosis is made between the twenty-eighth and the thirty-fourth week, the physician is certainly obligated to explain the situation with full implication to the patient and take into consideration the patient's decision regarding therapy. This consideration of a patient's decision should not be misconstrued as a shirking of responsibility on the physician's part. It is not, for there are many factors which influence the final decision. As soon as the physician is satisfied with the size of the fetus between the twenty-eighth and the thirty-fourth week the pregnancy should be interrupted by cesarean section and therapy as outlined below should be initiated. After the thirty-fourth week, immediate interruption by classical cesarean section is indicated. External x-ray (3,000 r) is started on the seventh to the tenth postoperative day with a lead shield used as protection for the wound. Central therapy with cobalt or radium in two applications to deliver 7,000 r to point A, follows external x-ray. A classical cesarean section rather than a low cervical cesarean section is indicated in an effort to stay away from the involved area as much as possible.

Therapy in First Six Months Post Partum.—It is obvious that a carcinoma of the cervix originally diagnosed during the 6 months post partum was certainly present during the pregnancy. Treatment should be given as if the patient had never been pregnant, and accordingly central therapy with cobalt or radium with 7,000 r delivered to point A is given first. External therapy, 3,000 r, follows. As will be seen later, treatment during the first 6 months post partum is not accompanied by a satisfactory survival rate.

Results

We realize that a statistical report from a series of only 28 patients may well be subject to error, but there are certain trends which are quite clear-cut and our impressions are in general agreement with those of Kistner and associates[5] who presented a statistical review of 136 cases.

TABLE IV. FIVE-YEAR SURVIVAL

STAGE	%
With Pregnancy.—	
I	62.5
II	33.3
III	0.0
Nonpregnant.—	
I	78.6
II	49.3
III	26.4

By reference to Table IV, it can be clearly seen that the 5 year survival rate for carcinoma of the cervix associated with pregnancy is less than that for the disease in the nonpregnant. The prognosis for a patient with a Stage III carcinoma is gloomy indeed, but this may be erroneous as there were only 4 patients with Stage III lesions in the total of 28 patients.

The current status of all patients in indicated in Table V. Of all these patients, 71.4 per cent are alive at this writing but 25 per cent are living with evidence of their original disease. The fact that, of the total 28 patients, 19 have registered since 1952 raises the percentages in the living column.

TABLE V. STATUS OF PATIENTS, 1940 TO 1957

	NO.	%
Living without disease	13	46.4
Living with disease	7	25.0
Total living	20	71.4
Dead	8	28.6
	28	100.0

Comment

It was our hope that this study would furnish information regarding the question as to whether the impact of pregnancy influences the survival rate when associated with carcinoma of the cervix. We believe that Tables VI and VII will help answer that question.

TABLE VI. PROGNOSIS BY TRIMESTERS

	FIRST AND SECOND TRIMESTERS				THIRD TRIMESTER AND 6 MONTHS POST PARTUM			
	NO.		%		NO.		%	
No. of patients	13				15			
Living without disease	8		61.5		3		20.0	
Living with disease	5		15.4	38.5	12		46.6	80
Dead			23.1				33.4	

Our preliminary impressions were that the patients who were found to have carcinoma of the cervix originally diagnosed during the first and second trimesters of pregnancy had a survival rate superior to that of patients whose diagnoses were delayed to the third trimester or in the 6 months postpartum period.

By inspection of Table VI it is seen that 61.5 per cent of the patients were living without evidence of the disease whose lesions were discovered in the first and second trimesters, as contrasted with 20 per cent discovered in the third trimester and in the first 6 months post partum. By the same token, patients who were found to be living with their disease varied from 15.4 to 46.6 per cent for the corresponding times of diagnosis.

Whether these differences in prognosis by trimester would be the same if there were more late-stage carcinomas in the third trimester and the 6 months post partum is a matter for conjecture. Table VII shows the breakdown of stages per trimester. There was an almost equal breakdown of Stage I and II carcinomas for the early and late trimesters.

TABLE VII. PROGNOSIS BY STAGES AND TRIMESTERS

STAGE	TRIMESTER				
	1	2	3	6 MONTHS POST PARTUM	
I	4	6	5	0	
11—					—12
II	1	0	3	4	
III	1	0	2	1	
IV	0	0	0	0	

The trend in prognosis as shown by trimester certainly is not intended to supplant the prognosis by stage, but rather to supplement it. It is also obvious that the longer carcinoma is present without being recognized, whether the

patient is pregnant or not pregnant, the worse the prognosis becomes, but when patients with early stages of carcinoma do poorly in the latter trimesters of pregnancy, one cannot help but wonder if the pregnancy does not contribute to the poor prognosis.

Until more experience is available with the radical surgical treatment of carcinoma of the cervix associated with pregnancy, irradiation, combining external and central approaches, will continue to be the treatment of choice.

Summary

Twenty-eight cases of carcinoma of the cervix associated with pregnancy are reviewed. Analysis of the results suggests that patients whose carcinomas are diagnosed in early pregnancy fare better than patients with carcinomas of comparable clinical stages which are diagnosed in late pregnancy or the postpartum period.

References

1. Carter, Bayard, et al.: Am. J. Obst. & Gynec. **71**: 634, 1956.
2. Danforth, W. C.: Am. J. Obst. & Gynec. **34**: 356, 1937.
3. Finn, William F.: J. M. Soc. New Jersey **52**: 61, 1955.
4. Hayden, Glen E.: Am. J. Obst. & Gynec. **71**: 780, 1956.
5. Kistner, Robert W., Gorbach, Arthur C., and Smith, George V.: Obst. & Gynec. **9**: 554, 1957.
6. Kottmeier, H. L.: Carcinoma of the Female Genitalia, Baltimore, 1953, Williams & Wilkins Company.
7. Macklin, Madge T.: J. Internat. Coll. Surgeons **21**: 365, 1954.
8. Marsh, Memoir, and Fitzgerald, Patrick J.: Cancer **9**: 1195, 1956.
9. McDuff, Henry C., Carney, Wilfred I., and Waterman, George W.: Obst. & Gynec. **8**: 196, 1956.
10. Montgomery, T. L.: South. M. J. **47**: 47, 1954.
11. Obst. & Gynec. Surv. **12**: 610, 1957.
12. Prystowsky, Harry, and Black, C. Bernard: Obst. & Gynec. **7**: 522, 1956.
13. Sadugor, M. G., Palmer, J. P., and Reinhard, M. C.: Am. J. Obst. & Gynec. **57**: 933, 1949.
14. Thornton, W. N., et al.: Am. J. Obst. & Gynec. **64**: 573, 1952.
15. Walters, William D., and Reagan, James W.: Am. J. Clin. Path. **26**: 1314, 1956.
16. Willson, J. R.: Am. J. Obst. & Gynec. **50**: 275, 1945.

ACUTE POLIOMYELITIS IN PRIVATE OBSTETRICAL PRACTICE*

MAHLON S. SHARP, M.D., LANSING, MICH.

OUR present-day concept of the relation of acute anterior poliomyelitis to obstetrics dates from the publication by Aycock[1] in 1941. Prior to this time, as a complication of pregnancy, it was rarely reported. McGoogan[2] in 1932 found only 5 cases in the world's literature and added 3 of his own. He believed with others that pregnancy probably conferred some degree of immunity. Brahdy[3] in 1933 reported 3 more cases and suggested that the reverse could be true, that is, that a greater susceptibility to the disease might be present. Taylor and Simons[4] in the Colorado epidemic of 1946 observed 25 cases in pregnant women. Gifford and Hullinghorst[5] in 1948 collected a total of 169 cases, adding one of their own. By 1953 Bowers and Danforth[6] were able to find 586 instances in the literature and reported 24 new cases.

Weinstein and associates[7] in 1950 found that 23 per cent of the patients with poliomyelitis between the ages of 20 and 40 years were pregnant, contrasted with a figure of 7 per cent which he arrived at for the incidence of pregnancy in this age group. Bowers and Danforth[6] emphasized the obvious difficulties in determining exactly how many women in the population were pregnant at any one given time, but agreed that poliomyelitis seemed to have a significantly higher incidence in pregnancy. Paula Horn's 20 year report concluded that for the year 1950 there was a 1.9 times higher rate for the pregnant than for the nonpregnant women in the age group from 15 to 44 years.[8] In an excellent paper from Connecticut, where menstrual history is requested in the required report form used by the State Department of Health, Rindge[9] found that 17.3 per cent of the women over 15 years of age were pregnant at the time they became ill.

Of course, various theories have been advanced to explain this increased association. The earliest one was that the hormones caused increased congestion of the respiratory mucous membranes and consequently an increased permeability to the virus. Experiments in giving quite large doses of estrogen to female monkeys[1] seemed, however, to increase their immunity. ACTH, it has been established, is increased in pregnancy[10] and, according to some workers, does increase the susceptibility in animals.[11] Exhaustion and fatigue possibly might be an explanation for the impressively high incidence in multiparas[9, 12, 13] (Table I).

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TABLE I. INCIDENCE OF POLIOMYELITIS IN PREGNANCY ACCORDING TO PARITY

SERIES	PRIMIPARAS
Siegel and Greenberg[12]	21.8
Anderson[13]	29.3
Bowers and Danforth[6]	25.9
Rindge[9]	11.4
This series	0

Horn[8] has replied to this that there is an impressively high incidence of multiparity in the female population. Siegel and Greenberg[12] reported that the increased incidence of poliomyelitis in pregnant women was directly related to the presence or absence of children in the household and that this usually was closely similar to the number of previous live births. Certainly it is impressive to note the relatively few primigravidas in the various reported series. There were none among the presently reported cases.

When called upon to give an explanation of why this disease in little more than a decade moved into the older age group (Table II), epidemiologists are not in complete agreement. One explanation is that modern plumbing and increased sanitation have permitted the whole population to grow to an older age level without exposure to and consequent immunization by the virus. In the years that the disease was known as "infantile paralysis," women had been immune from their own infancy, at which time they were exposed to the virus and either had the disease clinically or in most instances, if strong babies, merely acquired immunity.

TABLE II. DISTRIBUTION OF ACUTE POLIOMYELITIS ACCORDING TO AGE*

YEAR	UNDER 14 YEARS (%)	15-19 YEARS (%)	20 YEARS AND OVER (%)
1944	77.1	11.2	11.7
1945	75.9	10.6	13.5
1946	73.6	10.3	16.1
1947	72.7	10.5	16.8
1948	73.8	8.3	17.9
1953	68.2	8.9	21.9
1954	67.1	8.4	24.5
1955	65.1	9.0	25.9
1956	66.3	8.6	25.1

*From the Annual Statistical Review, National Foundation for Infantile Paralysis, 1956.

In reviewing the annual incidence of this disease in the general population (Fig. 1) it is evident that high years are followed by several years of reduced occurrence. This is due supposedly to an exhaustion of susceptibles or a high general immunity. According to this, it is evident that years 1949 to 1955 should have been followed in 1956 and 1957 by a very reduced number of cases.

There are some who advise caution in our enthusiasm for the program of immunization with the Salk and similar vaccines. The natural history of this disease makes immunization difficult to evaluate and there have been a disturbing number of poliomyelitis-like conditions in the groups who have received the vaccines.

The cases that we are here concerned with varied from very mild easily missed clinical manifestations to 2 fatal infections (Table III). Both fatal cases were acute manifestations in the postpartum period. Perhaps these deaths point to the role of fatigue in the maternal prognosis. The usual gravida tires most easily in the last trimester and to an even greater degree in the puerperal period when sleep is so often interrupted, irregular, and insufficient. Early discharge from the hospital, with the lack of domestic help, perhaps explains the fact that the mothers of this period are more fatigued.

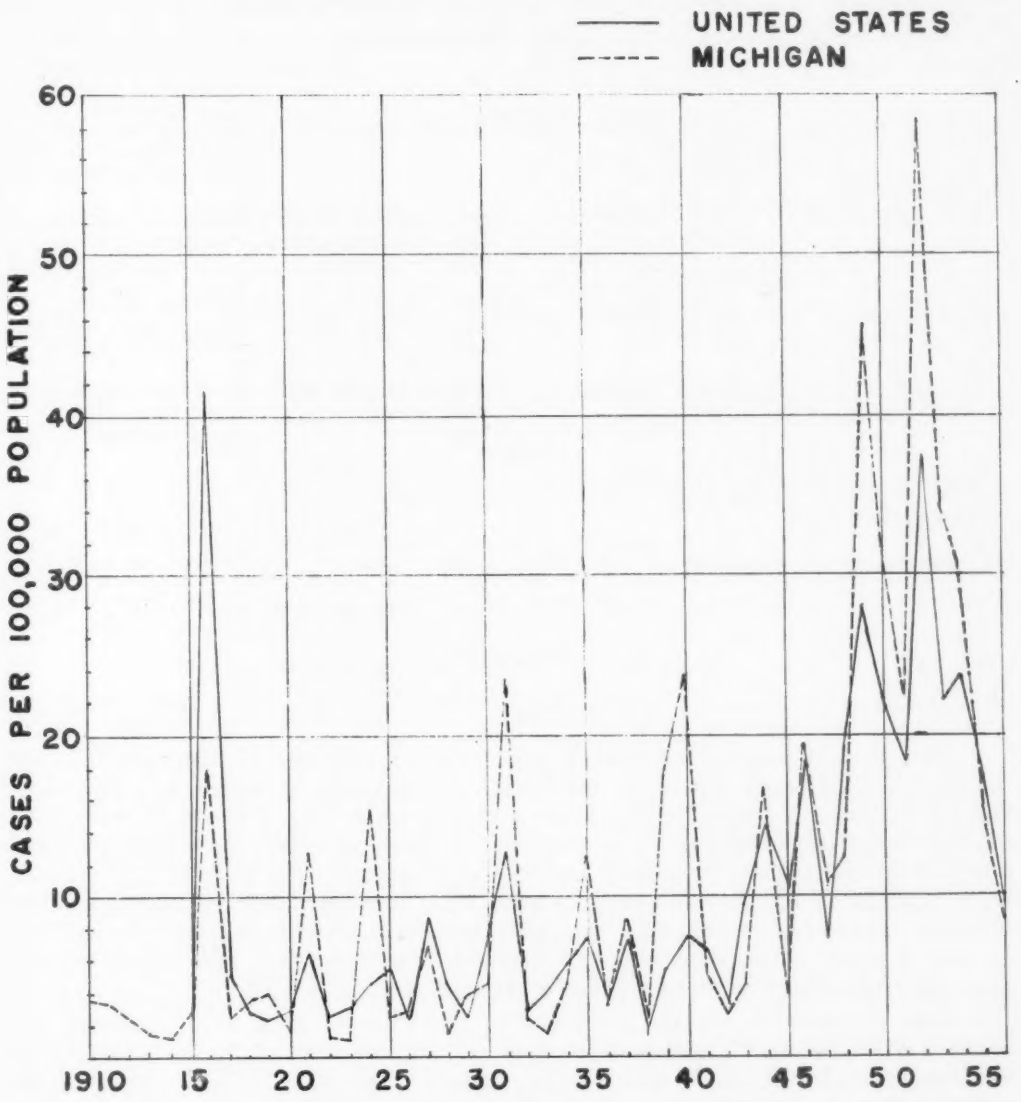


Fig. 1.—Incidence of poliomyelitis by year. (From Statistical Methods Section, Michigan Department of Health.)

Horn,[8] Weinstein,[14] and others have observed that the acutely ill patient withstands the exertion of labor poorly. Horn, in fact, believes that in the last 4 to 6 weeks of pregnancy there is an indication for termination of the pregnancy by cesarean section if the seriously ill patient's condition seems

to grow worse. An observation[15] has been made that in patients with paralysis who survive in general the degree of involvement is proportional to the amount of fatigue present at the onset. This seems to apply to those who develop paralysis in pregnancy as well.

TABLE III. NINE CASES OF ACUTE POLIOMYELITIS IN PREGNANCY

CASE	AGE	GRAVIDITY	PARITY	TRIMESTER	OUTCOME	SPECIAL CIRCUMSTANCES AT TIME OF ONSET
Fatal.—						
1	23	i	i	Post partum	Healthy infant	Anxious new mother. Stressful accommodation to firstborn
2	27	iii	i	Post partum	Healthy infant	Anxious new mother. Stressful accommodation to firstborn
Paralytic.—						
3	22	ii	i	Third	Severe paralyses. Delivered in respirator. Healthy infant	Sick child. Husband student
4	26	iv	iii	Second	Quadriplegic. Temporary paralysis of infant	Working mother. Three small children. Husband student
5	25	ii	i	Second	Residual in back and legs. Healthy infant	Apartment hunting in new town with 3-year-old child
6	25	iii	ii	First	Slight back weakness. Aborted	
Nonparalytic.—						
7	26	ii	i	Second	Full recovery. Healthy male infant	
8	27	ii	i	Third	Full recovery. Healthy female infant	
9	30	iii	ii	First	Full recovery. Healthy male infant	

Case 3 is of interest because it presented in 1949 the problem of delivery while in a respirator. A chest shell with battery-driven motor was used and the patient was taken by ambulance across town to the obstetrical suite of a general hospital. Before our anesthetist arrived to administer intratracheal anesthesia, the patient was delivered by low forceps of a normal male infant with pudendal block anesthesia. She was then rapidly returned to her Brinker respirator, which she was able to leave entirely several days later. It was 2 years later that Horn's[16] large series permitted generalizations to be made regarding the management of these seriously ill patients.

Horn's report[8] gives an incidence of 22 per cent total fetal wastage, including a 13 per cent abortion rate that seems consistent with the observation of Hunter and Millikan[17] and others. Horn reported 2 infant deaths from poliomyelitis contracted from the mothers neonatally. In none of her series was it believed that the disease was contracted transplacentally, although other authors[18, 19] consider this a possibility. Case 4, however, may represent such an instance. The infant lived and recovered from its varied nervous disorders and muscular weaknesses.

It is quite generally agreed that infants born of mothers who suffer the disease in early pregnancy are less well developed and of lower average weight even though they are carried to term. The infants of this small series

seem to bear this out with the exception of the infant in Case 9, who was the third child of a woman accustomed to bear large babies, and who had an unusually light case without sequelae at the end of the first trimester. None of the surviving patients seemed incapacitated for further childbearing (Table IV).

TABLE IV. SUBSEQUENT PREGNANCIES

CASE	PARITY	SEQUELAE	RESULTS
Paralytic.—			
3	iii	Multiple paralyses	Uneventful pregnancy. Healthy male infant, 7 pounds, 11 ounces
4	iii	Quadriplegic	Divorced, remarried. Therapeutic abortion six years later
5	iii	Back and one leg very weak	Uneventful pregnancy. Normal delivery of male twins, 7 pounds, 9½ ounces, and 7 pounds, 14 ounces
6	iv	Slight back weakness	Normal delivery of female infant, 5 pounds, 1 ounce
Nonparalytic.—			
7	iii	No residual	Spontaneous abortion
8	iii	No residual	Uneventful pregnancy. Healthy female infant, 7 pounds, 1 ounce
9	iii	No residual	No subsequent pregnancies

Summary

Nine cases of acute anterior poliomyelitis which occurred in a private obstetrical practice are presented.

A general observation is made that the state of fatigue in part determines the prognosis at the time of the acute illness.

References

1. Aycock, W. L.: New England J. Med. **255**: 408, 1941.
2. McGoogan, L. S.: AM. J. OBST. & GYNEC. **24**: 215, 1932.
3. Brahdy, M. B., and Lenarsky, M.: J. A. M. A. **101**: 195, 1933.
4. Taylor, E. Stewart, and Simons, J. M.: AM. J. OBST. & GYNEC. **56**: 143, 1948.
5. Gifford, H., and Hullinghorst, R. L.: AM. J. OBST. & GYNEC. **55**: 1030, 1948.
6. Bowers, V. M., Jr., and Danforth, D. N.: AM. J. OBST. & GYNEC. **65**: 34, 1953.
7. Weinstein, L., Aycock, W. L., and Feemster, R. F.: New England J. Med. **245**: 54, 1951.
8. Horn, P.: Obst. & Gynec. **5**: 416, 1955.
9. Rindge, M. E.: New England J. Med. **256**: 281, 1957.
10. Barnes, A. C.: Obst. & Gynec. **3**: 322, 1954.
11. Dunham, W. B.: J. Bact. **65**: 224, 1953.
12. Siegel, M., and Greenberg, M.: New England J. Med. **253**: 841, 1955.
13. Anderson, G. W., Anderson, G., Skaar, A., and Sandler, F.: Am. J. Hyg. **55**: 127, 1952.
14. Weinstein, L., and Meade, R. H., III: AM. J. OBST. & GYNEC. **70**: 1026, 1955.
15. Editorial: Brit. M. J. **2**: 1071, 1948.
16. Horn, P.: Ann. West. Med. & Surg. **5**: 93, 1951.
17. Hunter, J. S., Jr., and Millikan, C. H.: Obst. & Gynec. **4**: 147, 1954.
18. Schaeffer, M., Fox, M. J., and Li, C. P.: J. A. M. A. **155**: 248, 1954.
19. Shelokov, A., and Weinstein, L.: J. Pediat. **38**: 80, 1951.

Discussion

DR. JOSEPH C. WILLIAMS, Kansas City, Mo.—I should like to present 25 additional cases of poliomyelitis complicating pregnancy which were treated at the Kansas City General Hospital No. 1 from 1950 to 1953.

During this period there were 376 cases of poliomyelitis admitted to the hospital; 180 of these patients were females of whom 88 were in the childbearing age group. Twenty-five, or 29 per cent, of this group of 88 female patients were pregnant, which is a rather marked increase over the estimated incidence in pregnancy. Therefore, our group of patients substantiates the findings of other investigators that pregnant women seem to be more susceptible to poliomyelitis.

Not only was the pregnant woman seemingly more susceptible to poliomyelitis, but the incidence of bulbar extension was noted to be more common than in the nonpregnant group. Seven, or 28 per cent of the 25 pregnant patients had bulbar-spinal poliomyelitis, as compared to 11, or 17 per cent, of the 63 nonpregnant women. The mortality rate shows that pregnant women were less apt to cope with bulbar-spinal poliomyelitis successfully. The mortality rate was 71 per cent, as compared to 36 per cent in the nonpregnant group.

The onset of the spinal type was equally distributed among the trimesters of pregnancy, while the bulbar type occurred only in the second and third trimesters. Three of the 4 patients with bulbar poliomyelitis in the last trimester died. The seriousness of the bulbar-spinal type in the last trimester is noted by all observers with the exception of Horn, who reported that the incidence and mortality rate are similar for each trimester.

The fetal mortality in our series was 20 per cent, with one stillbirth, one abortion, and 3 deaths in utero. There were no neonatal deaths. Two postmortem cesarean sections were performed, one successfully. This was on a mother who died rapidly, while in the unsuccessful case maternal shock preceded death by 45 minutes.

Dr. Sharp has pointed out that the addition of fatiguing situations may have increased the susceptibility to and/or the severity of the infection of 5 of his patients. Since the essayist's series is composed of private patients, he was familiar with their personal lives, while in a review of the charts of clinic patients this type of information is notoriously lacking; but in our series there were 3 cases in which the onset of poliomyelitis was preceded by unequivocal states of exhaustion. All three of these patients were seriously ill, and like the essayist, I also question what might have been the outcome of these cases without the preceding states of exhaustion.

In view of the many excellent papers in the literature, the care of the pregnant poliomyelitis victim is well outlined and documented by most obstetricians with the exception of one point of contention. There is disagreement as to the indications, if any, for performing a cesarean section for nonobstetrical reasons in acute bulbar-spinal poliomyelitis with rapidly progressing paralysis and respiratory embarrassment. Horn, in her early observations, noted a high maternal death rate in this type of patient and therefore subsequently performed cesarean sections in 10 similar patients with only one maternal death. Hunter and Millikan from the Mayo Clinic later reported 5 cases which met Horn's criteria for interruption of the pregnancy by cesarean section. With spontaneous or induced vaginal delivery, however, only one maternal death occurred. In our series there were three cases which met Horn's criteria; each was treated in a conventional manner for poliomyelitis without thought of interrupting the pregnancy. One patient was delivered of a 4½ pound stillborn infant and then died 2 days later. The other 2 patients had postmortem sections. Our experience of a 100 per cent mortality in 3 cases would demand a more careful scrutiny of Horn's recorded experience in this category of patients, in an effort to evaluate the desirability of evacuation of the uterus in such cases. Our patients were hospitalized 5, 9, and 13 days prior to death, and cesarean section could have been considered in the early part of the hospital stay before the patient's condition became critical.

DYNAMIC INVESTIGATION OF PERINATAL MORTALITY*

James Hutchison Williams, M.D., John C. Ullery, M.D., Thomas E. Shaffer, M.D., and William A. Newton, Jr., M.D., Columbus, Ohio

(From the Department of Obstetrics and Gynecology, the Department of Pediatrics, and the Department of Pathology, The Ohio State University)

THE subject of stillbirth and newborn infant death is unparalleled in emotional impact. The prevention of fetal wastage is obviously desirable and the contributing causes are many and varied. The frequency of articles in the lay press is sufficient evidence of the keen public interest in the matter. Studies of stillbirth and neonatal death have been under way in various medical centers and in certain communities for some years. Recently the profession has become more generally interested, and many more studies have resulted. From such a variety of independent work a number of study methods is to be expected. It is the purpose of this essay to present a comprehensive report of a detailed program carried out at The Ohio State University Health Center, Columbus, Ohio, as a pilot plan for a county-wide study now under way in Franklin County, Ohio.

Since fetal salvage is both an obstetric and a pediatric problem and includes the prevention of both neonatal death and stillbirth, the term "perinatal mortality," which includes all fetal deaths associated with parturition, is logical and hereafter so used. The American Academy of Pediatrics and The American College of Obstetricians and Gynecologists, in order to effect uniformity in the study of this problem, have defined perinatal mortality as the death of any fetus, including both stillborn and liveborn, from 20 weeks' gestation through 1 week of extrauterine life. Such a definition does not include the cases of later neonatal death between the seventh and the twenty-eighth days of life which have been included in many studies. Inasmuch as 95 per cent of neonatal deaths occur in the first 7 days of life, the 7 day period seems sufficiently complete for ordinary analysis.

The Perinatal Health Committee

Perinatal mortality has been studied regularly in house staff conferences at the University Hospital, Columbus, Ohio, for several years. Since Jan. 1, 1956, however, every case of perinatal death has been studied in complete detail as a pilot plan for the over-all Franklin County study. During the

*Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

first year of this pilot study a total of 3,800 births occurred. In this group there were 63 stillbirths, 3,737 live births, and 82 neonatal deaths, a total perinatal mortality of 145. The perinatal mortality index was 38.2. This index is obtained by dividing the total number of perinatal deaths by the total number of births for the hospital. This is the figure upon which we should have some influence if our study and efforts produce beneficial results in future years.

To carry out this study, a Perinatal Health Committee was formed, composed of an obstetrician, a pediatrician, and a pathologist. It soon became apparent that the anesthesiologist was as vitally interested and as much concerned in a certain group of patients as were the first three members, and he is now an active member of the Committee. The nursing staff was also included. Any other interested persons may be members or participate in such a committee.

The organization of the study, we believe, is fundamental to its success. In the pilot study, résumés of the cases concerned have been prepared by the house staff once a month. Each case, after detailed review, is prepared in a reasonably simple fashion for presentation at the subsequent staff meeting a few days later. The résumés are then reviewed by the Committee at this preliminary meeting at which time all facets of the case are discussed and a preliminary classification is applied to each case. At this meeting the gross and microscopic pathology is reviewed to corroborate or correct the clinical diagnosis and cause of death. At this time it is possible to eliminate all the cases which have fairly obvious clinical and pathologic findings, and thus the staff meeting can be limited to those which are: (1) controversial, (2) of teaching interest, or (3) present problems of classification. The latter cases are then prepared for formal presentation at the staff meeting at which time final case analysis is made.

The several selected cases warranting such full staff consideration are presented with the care and detail of a clinicopathologic conference with complete autopsy material available. This monthly meeting has in attendance: obstetricians, anesthesiologists, pediatricians, a pathologist, nurses, house staff, and all senior medical students. Autopsy findings are vital in confirmation or correction of clinical diagnosis and identification of causes of death. (Autopsies were carried out on 138 of the 145 infants in this study.) There results a discussion of the pertinent clinical and anatomic findings in each case of fetal death, with amplification of any controversial points. Classification of responsibility is then carried out in a manner patterned after that of the maternal mortality studies. It has been our experience in this study that classification of responsibility forces each case discussion to a conclusion so that the decisions as to the final diagnosis and outcome are never thrown into a wastebasket classification.

Clinical Material

Perinatal death in many instances is the result of several factors. In most cases, however, a primary cause can be identified, and when so simplified the case material of this series is readily summarized (Table I).

TABLE I. CAUSES OF DEATH

Anoxia		36
Placenta previa	3	
Abruptio placentae	21	
Cord complications	4	
Related causes (marginal sinus, etc.)	8	
Birth trauma		3
Malformations		9
Toxemia		4
Erythroblastosis		5
Maternal diabetes		2
Other maternal pathologic conditions		3
Abnormal pulmonary ventilation		37
Atelectasis and/or hyaline membrane	28	
Pneumonia	6	
Other	3	
Abortions (weight under 1,000 grams)		34
Unexplained		12
Total		145

By complete analysis of the material, it has been possible to apply a primary classification of responsibility patterned after that of the standard maternal mortality studies and to divide the cases into two gross groups for analytical purposes. First, there is a nonpreventable group, in which 68 per cent of the cases were classified primarily. The second group, the preventable group, was broken into two parts: the first part, those in which there was primarily patient responsibility (P_1), 12 per cent; and the second part, those in which there was personnel responsibility (P_2), 20 per cent. Needless to say, these are primary classifications, and in several instances secondary classifications were necessary, sometimes this secondary classification being quite important. In an effort at self-criticism, however (and this point bears considerable emphasis), the perinatal deaths have always been classified as preventable even when only possibly preventable. As a result, some deaths have been classified as preventable (either patient or personnel) even though the infant weighed considerably less than 1,000 grams or some nonpreventable factor associated with the death was obviously finally responsible.

TABLE II. CAUSES OF NONPREVENTABLE DEATHS

Extreme immaturity	24
Complicating disease	19
Complication of pregnancy	37
Developmental defect	8
Unclassified	10
Total	98 (68%)

Nonpreventable Deaths

A breakdown of the nonpreventable cases appears in Table II. There were 24 babies in the group of extreme immaturity. These were the infants under 1,000 grams in whom no other factors of significance were found. The complicating disease processes included hyaline membrane disease in the infant, maternal diabetes, and intercurrent disease in the mother when properly treated. Pregnancy complications, of which there were 37 cases, included toxemia, abruptio placentae, premature rupture of membranes, and other complications of pregnancy in which there was adequate treatment of any preventable factor. There were 8 infants with developmental defects incompatible with

life. The 10 unclassified deaths included those of macerated stillborn infants for whose obvious intrauterine deaths there was no clinical or pathologic explanation.

The group of patient responsibility cases included 18 perinatal deaths. (Table III). Of these, there were three infants lost where there was clear failure to heed the physician's advice and 15 in which there was failure on the part of the patient to seek medical care at a time when it was felt it might have made some difference in the outcome of the pregnancy. There have been included in this group six deaths wherein the failure to seek medical care probably had no direct effect upon the infant's death but in which the failure to seek care did represent far less than ideal management.

TABLE III. PATIENT RESPONSIBILITY

Failure to seek care	15
Failure to heed advice	3
Total	18 (12%)

The eventual clinical benefits of such a study result from analysis of the cases which are found to have factors of personnel responsibility (Table IV). All cases with any possible preventable factors were included in this group and, therefore, the 29 deaths include 8 in which there were other factors present. These, no doubt, caused the infant's death regardless of the responsibility factors in the various areas of management. A breakdown of these 29 cases as to the preventability factors in each of the groups concerned is given in Table IV.

TABLE IV. PERSONNEL RESPONSIBILITY

Prenatal management	1
Obstetric management	17
Anesthetic management	6
Pediatric management	4
Nursing management	1
Total	29 (20%)

Preventable Deaths

Preventable factors associated with the mothers' prenatal management were anemia and weight gain. In one case there was severe anemia, insufficiently treated during the prenatal course. This neglect was felt to have been a definite factor in the development of abruptio placentae. Excessive weight gain was present in another case as a secondary factor.

Obstetric management at the time of labor and delivery was considered responsible or contributory in 17 cases (Table V). The preventability factors included overmedication prior to general anesthesia and/or sedation in the case of premature or distressed infants. In these, lighter premedication with local or regional anesthesia would, undoubtedly, have been preferable. Failure to act upon a persistent fetal heart rate below 100 was significant in 2 perinatal deaths. More dramatic intervention, such as cesarean section, might have saved an infant whose intrauterine bradycardia and irregular heartbeat were significant. Amnionitis at term occurred in several patients, but in 2 cases it was outstanding and was shown pathologically to be the cause of the deaths. One such death occurred in a multiparous patient at term with ruptured membranes in whom induction of labor might have avoided the loss of time and development of amnionitis. Borderline pelvic capacity was of significance in one. The

calculation of the estimated data of confinement and management of the second stage of labor were important in 2 others. In one of these a delay of more than 2 hours from complete dilatation of the cervix to delivery resulted in a perinatal death established by autopsy as typical of fetal embarrassment in utero. Mismanagement of erythroblastosis was very significant in a recent fetal death in which the obstetrician had a responsible part. The cord was milked at the time that this infant was born. Inasmuch as milking the cord toward the baby at the time of birth of an erythroblastotic or potentially erythroblastotic infant may raise the circulating blood volume sufficiently to produce heart failure, this was felt to be a significant factor and, therefore, was considered obstetrically preventable.

TABLE V. PREVENTABLE FACTORS IN MANAGEMENT

Obstetric	17
Overmedication	
Misinterpretation of fetal heart tones	
Amnionitis at term	
Borderline pelvic capacity	
Calculation of estimated date of confinement	
Management of second stage	
Erythroblastosis	
Anesthetic	6
Spinal hypotension	
Injudicious general anesthesia	
Unnecessary delay	
Pediatric	4
Septicemia (especially Pseudomonas)	
Pulmonary defects (undetected for want of x-ray)	
Erythroblastosis	

Hypotension from spinal anesthesia was a factor in one neonatal death classified under anesthetic management (Table V). The depressed infant subsequently developed an atypical pulmonary hyaline membrane and died. Injudicious general anesthesia was a factor in several cases, particularly of prematurity. In one, pentothal soduim was used for elective repeat cesarean section in which there occurred unexpected delay, resulting in administration of an excessive amount of general anesthetic prior to the delivery of the infant. (Any aspect of anesthesia, whether administered by the anesthesiologist or the obstetrician or dictated by the anesthesiologist or the obstetrician to other personnel, has been included in the anesthetic management group.) Unnecessary delay occurred in the induction of anesthesia in one case in which there was felt to be an anesthetic factor in the infant's neonatal death.

There were 4 cases in which pediatric factors (Table V) were felt to be primarily responsible. Septicemia due to the Pseudomonas organism was significant in 3 cases. We have found the injudicious use of inhalation mist and other sources of potential Pseudomonas infection is to be avoided. Although broad-spectrum antibiotics protect against a multitude of organisms, it is quite apparent that other more insidious sources of infection may produce Pseudomonas septicemia and death, particularly in the premature infant, who is especially vulnerable. Undetected pulmonary lesions were felt to be partially responsible in one or 2 cases, inasmuch as x-rays should have been taken earlier to detect the presence of a diaphragmatic hernia. Erythroblastosis was the assigned cause of death in one case in which there was delay in lowering the venous pressure of the newborn infant of an affected mother. Earlier rapid action and follow-up of laboratory work might have saved the infant.

Nursing management was felt responsible for only one case in which there was aspiration at tube feeding.

Comment and Conclusions

It has been the thesis of this study that immediate review of all cases is imperative. If the cases which occur in any given month are prepared for staff presentation the following month, small but often vitally important facets of the case are seldom overlooked. Investigation by a committee of active staff members elicits sometimes unrecorded data and makes the case studies more accurate. The committee's review of pathologic findings further permits reinvestigation of the clinical background of cases in which the autopsy findings are at variance with the clinical impressions. It is the unanimous opinion of the committee members and staff that this method of study is definitely more accurate and certainly more informative from an educational standpoint than review of cases from questionnaire data.

From this short time of study alone there have evolved: (1) a complete case study of all fetal deaths; (2) a free exchange of ideas between obstetricians, pediatricians, anesthesiologists, and pathologists; (3) objective self-criticism without attention to personalities; and (4) re-appraisal of medical management, particularly in the areas of labor, delivery, and the newborn infant. The latter already includes: (a) greater attention to the fetal heart rate in utero, (b) a decrease in premedication, particularly if a small infant is anticipated, (c) extension of the use of conduction anesthesia, (d) care to avoid amnionitis, and (e) greater speed and care in the management of erythroblastosis fetalis.

Medical education on the attending staff level as well as house staff and student level is the end toward which this study was primarily aimed. It is in this area that the greatest immediate good can be realized and it is only by local evaluation of cases on the level of the individual hospital staff that all facets of the perinatal deaths can be properly elicited and evaluated.

By application of this format, modified to fit the individual hospital, the study is currently in progress in the major Columbus hospitals which have obstetric services. These hospitals utilize their individual facilities to the appropriate degree. Their staff conference presentations are in some instances less elaborate and on the smaller services are presented only quarterly. A simple case report form is in use for central analysis of data from the participating hospitals. It includes a simple tabulation of: (1) vital statistical data, (2) obstetric history, (3) obstetric diagnosis, (4) pediatric diagnosis, (5) pathologic diagnosis, and (6) perinatal mortality classification.

These data are confidential and available for study to the participating hospitals only.

This county study has no official connection with the Health Department, University, or government agency. It is sponsored jointly by the Columbus Obstetric-Gynecologic Society and the Central Ohio Pediatric Society. Participation is completely voluntary. This, we believe, is vital to the success of such a study.

This dynamic type of study has already produced positive results in our hands. We believe it will do so for the obstetric staffs of other hospitals.

Summary

A study of the problem of perinatal mortality has been undertaken on a clinical level at The Ohio State University Health Center in Columbus, Ohio.

The pilot study for the calendar year 1956 is herewith reported and analyzed. Twenty per cent of the cases were found to have some significant factors in management which might have altered the outcome as to perinatal death.

The format of study here used has been highly successful and is worthy, in our opinion, of continued use and expansion. The voluntary nature of the study is worthy of emphasis. The month-by-month analysis of cases by the staff concerned has been found to be far more rewarding than analysis by a central committee based on detailed questionnaire reporting.

Discussion

DR. HAROLD W. LONGYEAR, Royal Oak, Mich.—As obstetricians, our major interest in the past has been the reduction of maternal deaths. We have instituted widespread maternal death studies and have watched with satisfaction their influence on the declining maternal death rate. It now appears that some of us have been somewhat unmindful of the baby. This one-sided interest cannot persist. Dr. Williams has pointed out that the lay press is actively agitating for a similar reduction in perinatal mortality. We must accept our responsibility; we should not be forced to it by the lay press.

As obstetricians we can take pride in finding that many features of maternal death studies are equally valid in perinatal mortality studies.

Accurate compilation of data is essential. At times even such basic information as the time of death, as well as the immediate condition of the infant, is missing. The obstetrical record rarely has any information of value to the pediatrician. Too much space is allotted to traditional but irrelevant past history and too little to details of the current pregnancy. For proper study and evaluation, data must be collected quickly while the details are still vivid in the minds of the attending team.

Committee review of the data in open meeting assures careful consideration and complete discussion. This is particularly true when the committee includes representatives of other specialties as well as pediatrics and obstetrics.

Precise determination of the cause of death is essential for classification. Assignment of preventability and responsibility focuses attention upon the lessons to be learned from the study, and keeps it from bogging down in a morass of inconclusive data. To be most effective, responsibility and preventability must be determined on the basis of the academic ideal.

Currently there are several different types of perinatal death studies in progress. There are those which sample statistics from key hospitals, like a medical Gallup poll. This scheme has been used in Detroit for the past five years. Here it has been ineffective because it could not secure the necessary details to establish cause and preventability. There are city-wide surveys such as that recently reported from New York. The institutional type of survey, as reported by Dr. Williams, appears to be most effective but requires a well-rounded and interested house staff, and has the limitation of being confined to an institution whose standards and capabilities are superior.

THE INDICATIONS FOR CONSERVATIVE THERAPY FOR INTRAEPITHELIAL CARCINOMA OF THE UTERINE CERVIX*

JAMES S. KRIEGER, M.D., AND LAWRENCE J. MCCORMACK, M.D.,
CLEVELAND, OHIO

(From the Departments of Obstetrics and Gynecology and of Pathology, The Cleveland Clinic Foundation, and The Frank T. Bunts Educational Institute)

IN THE mind of the physician, carcinoma in situ of the uterine cervix (preinvasive or intraepithelial carcinoma, or Bowen's disease) although classified as Stage 0 carcinoma, nevertheless has taken on much of the aura of invasive carcinoma. Generally accepted optimal therapy[1-4] consists of total hysterectomy and upper vaginectomy with or without conservation of the ovaries. Irradiation and radical surgical procedures have been recommended for selected cases, while conization has been cautiously suggested only when it is desired to preserve the reproductive function. Conization, according to Peightal and associates,[5] Younge,[6] and Carter and associates,[7] might be adequate for treatment as well as diagnosis, provided that specific criteria are rigidly met.

This report presents our experience and some preliminary conclusions that we have drawn in the course of diagnosing and treating 114 cases of cervical carcinoma in situ at the Cleveland Clinic, from January, 1950, to January, 1957. From a survey of the data, we have attempted to ascertain the necessity for routine hysterectomy in the treatment of cervical carcinoma in situ.

First, we shall define the term *carcinoma in situ* of the uterine cervix. To us, it signifies a major cellular abnormality that has all of the histologic characteristics of true carcinoma but does not extend beyond the confines of the normal epithelial layer (Fig. 1). We agree with Fennell and Castleman[8] who consider glandular involvement noninvasive so long as the stroma has not been penetrated (Fig. 2).

Diagnosis

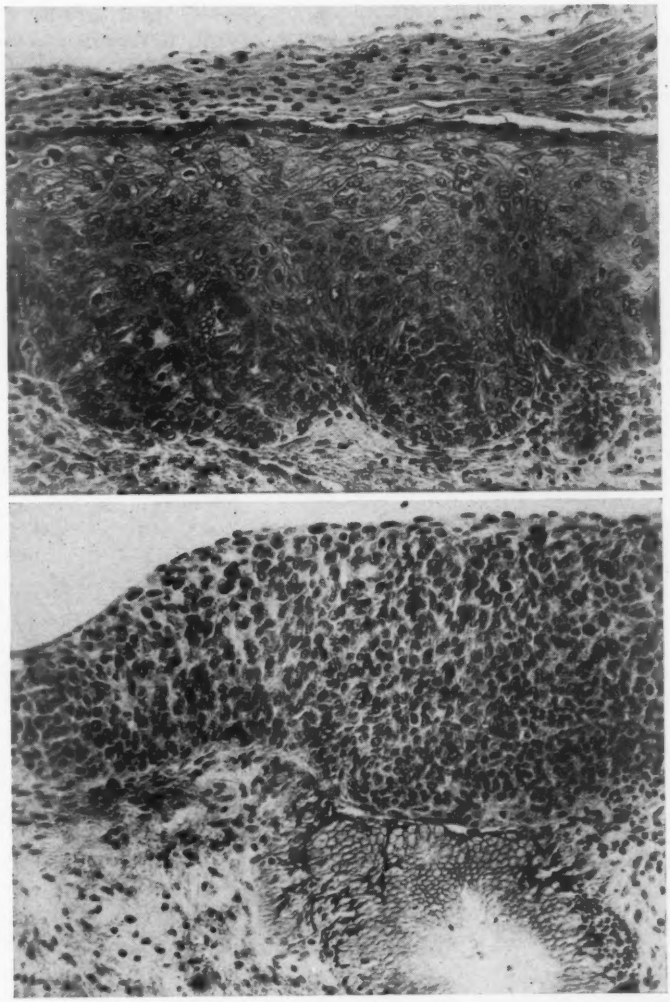
Since carcinoma in situ is invisible to the naked eye, the majority of cases are first suspected as a result of cervical spread studies. In the Pathology Laboratory of the Cleveland Clinic, 22,716 cervical cytologic specimens have been studied,[9] with the finding of 104 cases of invasive carcinoma and 112 cases of carcinoma in situ. The cytologic false negative rate, calculated on the total number of histologically proved cases, is 4 per cent. This means that

*Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

when a positive cytologic diagnosis is made in our institution, the chance of its being substantiated histologically has been 24 in 25. The cytologic differentiation between invasive and intraepithelial carcinoma is less precise[10]: of 99 cytologic specimens diagnosed as representing invasive carcinoma, 29 proved to be intraepithelial on histologic study; of 42 cytologically intraepithelial specimens, 6 were found to be invasive histologically.

We use the cervical spread routinely for the clean, normal-appearing cervix. For the abnormal cervix we use the spread technique and multiple biopsies. Sixty-five of the 114 cases were first suspected from routine cervical spreads (Table I); 28 cases were diagnosed on the basis of spread and biopsy; 21 cases were identified incidentally to the diagnosis of other disease.

A.



B.

Fig. 1.—Carcinoma in situ of the cervix uteri. *A*, Area of external cervical os showing nuclear irregularity, abnormal mitotic activity, and parakeratosis. On biopsy alone this area might be considered by others as dysplasia. *B*, Endocervical canal area on same section as *A*. Note absence of polarity, sparse cytoplasm, and nuclear irregularity with crowding. (Hematoxylin-eosin-methylene blue. ×245; reduced ⅙.)

TABLE I. METHODS OF DETECTION OF CERVICAL CARCINOMA IN SITU IN 114 CASES

METHOD	NO. OF CASES
Cervical spread, routine (clean cervix)	65
Cervical spread and biopsy (gross cervical lesion)	28
Biopsy only	7
Conization—incidental finding	13
Hysterectomy—incidental finding	1
Total	114

When there is no visible cervical abnormality and the cytologic study reveals abnormal or dubious cells, a sharp-knife conization is done in preference to random biopsy or repeated cervical spreads. If, on inspection, abnormality is evident, a biopsy is done. If the biopsy specimen is free of invasive carcinoma, a so-called radical conization is the next diagnostic step. We do not believe that random or quadrant punch biopsy specimens are sufficient to rule out the presence of carcinoma in situ or of coexistent invasive carcinoma. Since carcinoma in situ often arises in the endocervix, it is imperative that this area be included in any conization. Conization is a hospital procedure that requires general anesthesia. Cold conization is done with a No.10 Bard-Parker knife; it is followed by cautery conization with the Liebel-Flarscheim apparatus; and final hemostasis is accomplished with a ball-point cautery. The conization *must* be done prior to cervical dilatation.

The conization specimen is reduced to serial blocks, and usually at least 12 step-sections are examined microscopically. Study of this number of sections insures an accurate diagnosis of carcinoma in situ or of invasive carcinoma, and at the same time makes possible a close estimate of the extent of the lesion, excluding in so far as possible invasive carcinoma (Fig. 3). Ten to 15 per cent of histologically invasive carcinomas of the cervix present no gross morphologic evidence of their presence and can be detected only by cytologic studies.

Treatment

Until late in 1951 our usual form of treatment for cervical intraepithelial carcinoma consisted of total hysterectomy 6 weeks after diagnosis by conization. The lapse of 6 weeks was to allow time for thorough pathologic evaluation and complete healing of the cervix. Six weeks seems to be an adequate interval in which to evaluate the efficiency of conization. Patients who were considered poor surgical risks and those who were very young were treated with the above-outlined conization technique and then were followed with repeated cytologic study.

TABLE II. TREATMENT OF CERVICAL CARCINOMA IN SITU IN 114 CASES

TREATMENT	NO. OF CASES
Radical conization	65
Conization and hysterectomy	28
Conization and trachelectomy	2
Biopsy and hysterectomy (or trachelectomy)	10
Hysterectomy	2
Radium therapy	2
None—consultation only	5
Total	114

Since 1952, conization has been the treatment of choice in the absence of other disease that dictates hysterectomy. A patient is followed by cytologic

methods alone if (1) the lesion is noninvasive in the conization specimen, (2) the cervix remains patent following conization, and (3) repeated spreads remain negative. Papanicolaou spreads are obtained upon healing of the cervix, at 3 months, at 6 months, and every 12 months thereafter.

Table II summarizes the various treatments used. Multiple biopsies are an inadequate substitute for prehysterectomy conization. Irradiation treatment seems to be too drastic for this condition, though on rare occasions it has been used. In the best regulated practices an occasional case will be discovered incidentally after hysterectomy for other disease.

Results

Our results have been analyzed with a view to learning the effectiveness of radical conization, used either alone or with hysterectomy in treating cervical carcinoma in situ, and to answer if possible the question: "Is hysterectomy a therapeutic necessity in cervical carcinoma in situ?"

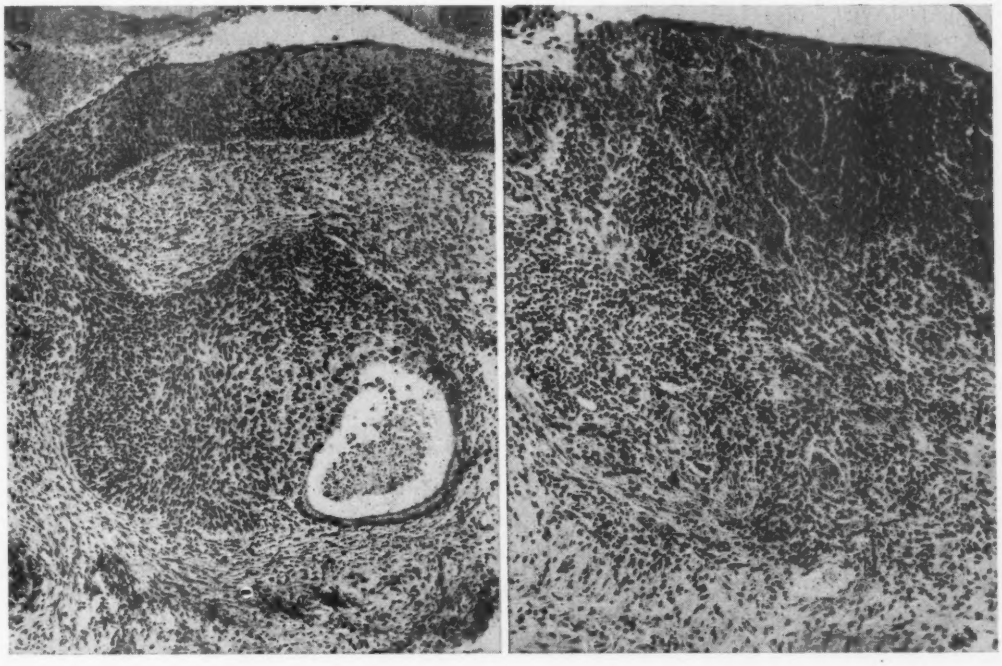


Fig. 2. Fig. 3.

Fig. 2.—Glandular involvement in carcinoma in situ of cervix uteri. (Hematoxylin-eosin-methylene blue. ×80; reduced ⅙.)

Fig. 3.—Early invasive squamous-cell carcinoma of the cervix uteri. Note change in cellular type to one with more cytoplasm. Endothelium-lined spaces also are invaded. (Hematoxylin-eosin-methylene blue. ×125; reduced ⅙.)

Twenty-eight patients were treated with conization and subsequently, in 6 weeks, hysterectomy. Two patients who had carcinoma in situ in a cervical stump were treated with conization and later with trachelectomy. In this group of 30 patients, 26 had no residual disease in the excised cervix and 4 had evidence of persistent carcinoma in situ. The hysterectomy had been performed in 3 of these because of the evidence of unusually extensive disease in the conization specimen (Table III).

Sixty-five patients had radical conizations as definitive therapy (Table II). Four patients have been lost to follow-up without postoperative cytologic

studies. Sixty-one patients have been followed for from 6 months to 7 years, and each has had a minimum of two postoperative cytologic spreads. Eight patients have been followed for more than 5 years; 23 patients for more than 3 but less than 5 years; 30 patients for less than 3 years (5 of these patients are at present lost to follow-up after 1 to 2 years). Cervical spreads have been negative repeatedly in all but 2 instances. In one of these, atypical cells were persistent despite two conizations; the cervix, after hysterectomy, did not reveal the source of those cells. In the other, dysplastic cells were demonstrated on the last two examinations—2 years after conization. This patient may come to hysterectomy.

Complications have occurred 7 times after conization. They have consisted of superficial overgrowth of epithelium with closure of the cervical os in 6 instances and in one instance vesicovaginal fistula. Two patients with closure of the cervix were treated in the office by incision and dilatation; 4 were hospitalized for the procedure. (One dilatation was unsuccessful and hysterectomy has been advised.) The vesicovaginal fistula healed uneventfully after transvaginal repair.

TABLE III. A RETROSPECTIVE EVALUATION OF CONIZATION BASED ON FINDINGS AT SUBSEQUENT HYSTERECTOMY OR TRACHELECTOMY

FINDINGS		NO. OF CASES
Specimen negative for carcinoma in situ		26
Residual carcinoma in situ		4
In situ lesion present in all blocks at conization	1	
Multicentric lesion at conization	1	
Present in curettings at conization	1	
Microscopic focus on 1 block in residual specimen; hysterectomy 3 days after conization	1	
Total		30

Comment

Our choice of therapy for cervical carcinoma in situ has undergone change in the past 7 years, as basic factors have become defined. Our current belief is that treatment can be individualized without undue risk to the patient's future health. We depend on cytologic study for the detection of otherwise unsuspected carcinima in situ; therefore it seems entirely reasonable to continue to rely on cytologic study in assessing the adequacy of conization. This method, it is true, does require the patient's cooperation and an access to well-organized facilities for cytologic study. Even when hysterectomy with upper vaginectomy is performed in the treatment of cervical carcinoma in situ, persistent or recurrent disease may be found at a later date in the vaginal vault. Te Linde, Galvin, and Jones[11] report one case and cite 3 others. They are observing 2 other patients who have positive cytologic findings after hysterectomy. Consequently, postoperative cytologic studies are necessary in evaluating any treatment used either for preinvasive or for invasive carcinoma of the cervix.

We believe that the patient's age has little bearing on the choice of treatment. It has often been suggested that the young woman who desires more children can be adequately treated with conization and followed by spreads, while the older woman who has fulfilled her reproductive role should be treated with

hysterectomy. This approach seems to us to be entirely inconsistent in view of the cervical trauma that is incurred during pregnancy and in labor. The younger woman has also a longer life expectancy in which to develop further lesions of the cervix. If conization can be selectively and safely employed in the young woman, this treatment should be adequate for the older one.

Other facts lend support to the validity of these conclusions. Carcinoma in situ by definition is a noninvasive lesion and consequently—provided that the diagnosis is correct—the lesion should be curable by local therapy. The stumbling block here lies with the pathologist's inability to examine all of the excised tissue. Physicians in general are rightfully fearful of undertreating carcinoma. They receive considerable lay support in this concept because of the overwhelming fear that a diagnosis of carcinoma and its implications arouse in people in general. Local excision, however, is generally agreed to be completely adequate therapy for Bowen's disease, a comparable lesion occurring in skin.

At present we cannot be sure that carminoma in situ actually is capable of becoming truly invasive carcinoma. The two diseases often coexist, but mere coexistence is no proof that actual transition from one type to the other took place. Most studies offering evidence of the invasive potential of carcinoma in situ have been retrospective in nature (groups of patients with invasive carcinoma have been studied to determine the incidence of pre-existing carcinoma in situ). Te Linde, Galvin, and Jones[11] recently presented such a study. Martzloff in the discussion of their report[11] points out the risk of drawing sweeping conclusions from such studies. Saphir[12] recently pointed out that there is reasonable doubt that carcinoma in situ will invariably become invasive. He believes that when invasive cervical carcinoma occurs after cervical carcinoma in situ has been diagnosed there well may be some question as to the accuracy of the original diagnosis, or that the invasive carcinoma may be coincidental. Kottmeier[13] cited the fact that until 1953, despite voluminous writing on the subject, only 58 cases had been recorded in which invasive carcinoma was present after prior-existing cervical carcinoma in situ.

Cervical carcinoma in situ is not always a clear-cut pathologic entity, and therefore is subject to great diversity of opinion among pathologists. In Siegler's[14] study, 20 specimens taken from clincally normal cervices were reviewed independently by 25 pathologists; they did not agree unanimously on the interpretation of any slide: 10 pathologists called at least 7 slides positive, while 6 pathologists found only one or no slide positive for carcinoma in situ. Pathologists differ among themselves because of the lack of rigid minimal pathognomonic criteria for the diagnosis. The degree of epithelial dedifferentiation, nuclear irregularity, and hyperchromatism, and the amount of cytoplasm present are subject to different interpretations by the individual physicians, and none has been able to communicate adequately his diagnostic convictions in this matter.

The diagnosis of coexisting invasive carcinoma likewise presents a problem. Extension to the necks of the glands may be marked but entirely controllable

by conization if the excision includes all of the gland-bearing area. It is our belief that early invasion has occurred when cell nests become irregular in size and shape and lack sharp definition from adjoining stroma; often, the histopathologic change is to a larger type of cell, and endothelium-lined channels contain tumor cells (Fig. 3).

With the general lack of agreement among pathologists concerning the diagnosis of carcinoma in situ, it is apparent that we are confronted with a condition that does not yet have precise boundaries of definition and so will continue to cause considerable confusion and difference of opinion. Consequently, clinicians should be careful to avoid dogmatism in their concept of this disease. It is likely that on tenuous grounds a great number of women have been simultaneously subjected to hysterectomy and psychologically traumatized by the fear of carcinoma.

On the basis of the available information, we believe that hysterectomy is not a therapeutic necessity in treating cervical carcinoma in situ. Treatment can be individualized—usually limited to radical conization with systematic cytologic follow-up. Hysterectomy can be reserved for (a) those patients who have persistent positive cytologic evidence of disease after radical conization, (b) those who cannot be followed by spread because of closure of the cervix, and (c) those who have other coincidental uterine disease.

Physicians who answer affirmatively our question, "Is hysterectomy a therapeutic necessity?" can be of aid in solving the query for those of us who are negatively inclined, by slightly modifying their approach, and this does not entail any compromise of therapy. If they will record the data in following this sequence: (1) carry out radical conization, then (2) wait 6 weeks before performing hysterectomy, then (3) carry out prehysterectomy cytologic studies, and then (4) have the excised uterus carefully studied, a considerable amount of information can be amassed in a relatively short period. Then, in another 10 years we should be in a position to judge more accurately the extent of treatment needed for cervical carcinoma in situ.

Summary

A series of 114 cases of carcinoma in situ of the cervix was analyzed for diagnosis and treatment.

In 30 of these, radical conization was followed in 6 weeks by total hysterectomy or its equivalent. Twenty-six specimens were histologically negative for residual disease following hysterectomy.

Sixty-five patients were treated only by radical conization; one subsequently underwent hysterectomy; 4 have been lost to follow-up; 61 have been followed with cytologic techniques for from 6 months to 7 years.

Conclusions

1. Treatment should be individualized and hysterectomy not considered to be a therapeutic necessity. In the majority of cases radical conization with systematic cytologic follow-up has been sufficient treatment.

2. Hysterectomy is reserved for those patients in whom cervical spreads remain positive after conization, the cervix closes and renders spreads unreliable, or other major uterine disease is present.

3. Those who favor hysterectomy routinely can contribute to our information regarding necessary treatment by using an approach outlined in the report.

References

1. Carter, B., Cuyler, K., Thomas, W. L., Creadick, R., and Alter, R.: Am. J. Obst. & Gynec. **64**: 833, 1952.
2. Morton, D. G., Zeldis, L. J., and Monk, A.: West. J. Surg. **63**: 185, 1955.
3. Harris, J. H., and Peterson, P.: Am. J. Obst. & Gynec. **70**: 1092, 1955.
4. Ross, R. A.: Am. Surgeon **20**: 1096, 1954.
5. Peightal, T. C., Brandes, W. W., Crawford, D. B., Jr., and Dakin, E. S.: Am. J. Obst. & Gynec. **69**: 547, 1955.
6. Younge, P. A.: In Homburger, F., and Fishman, W. J., editors: The Laboratory Diagnosis of Cancer of the Cervix, New York, 1956, S. Karger, pp. 16-20; disc. 21-22.
7. Carter, B., Cuyler, W. K., Kaufmann, L. A., Thomas, W. L., Creadick, R. N., Parker, R. T., Peete, C. H., Jr., and Cherny, W. B.: Am. J. Obst. & Gynec. **71**: 634, 1956.
8. Fennell, R. H., Jr., and Castleman, B.: New England J. Med. **252**: 985, 1955.
9. Krieger, J. S., and McCormack, L. J.: Cleveland Clin. Quart. **24**: 137, 1957.
10. McCormack, L. J., Belovich, Doris, and Krieger, J. S.: Am. J. Clin. Path. **28**: 179, 1957.
11. Te Linde, R. W., Galvin, G. A., and Jones, H. W., Jr.: Am. J. Obst. & Gynec. **74**: 792, 1957.
12. Saphir, O.: Obst. & Gynec. **9**: 368, 1957.
13. Kottmeier, H. L.: Carcinoma of the Female Genitalia, Baltimore, 1953, Williams & Wilkins Company, p. 213.
14. Siegler, E. E.: Cancer **9**: 436, 1956.

Discussion

DR. KENNETH E. COX, Kansas City, Mo.—In the interests of conservatism we[1] presented a paper before this society 9 years ago suggesting the establishment of a registry to further the cause of precision in diagnosis of these lesions. Our emphasis was upon completing the diagnostic routine before institution of any therapy.

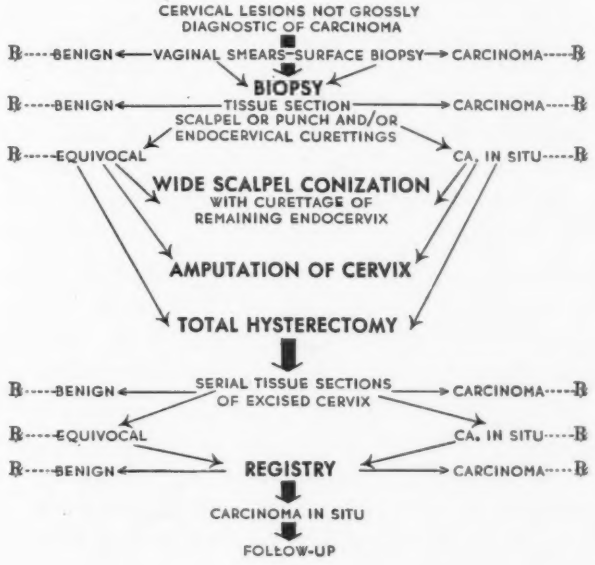


Fig. 1.

In Fig. 1 the heavy arrows emphasize the succession of diagnostic steps which may progress through hysterectomy. The ℞'s caution that further diagnostic steps are necessary

for precision, and that therapy should not be undertaken at this phase of the diagnostic routine. Hysterectomy for these lesions is always preceded by conization.

The addition of Stage 0 to our classification has grouped together lesions which run a spectrum all the way from "equivocal benignancy" to "equivocal malignancy." It is in the zones of overlapping between the stages that the answer to the question propounded by the title of this paper must be sought.

The addition of a Stage "00" is our suggestion to emphasize this point. A conservative trend of thought is directed toward the possibility of the "0" lesion being a "00," a completely benign one, whereas radical thinking is concerned with the possibility of a Stage 0 lesion being or becoming a Stage I. Conservative thought emphasizes the expected absence of metastasis in these very early microscopic cancers, while radical thought emphasizes the possibility of "early microscopic invasion" elsewhere in the cervix.

Reference

1. Cox, Kenneth E., Buhler, Victor B., and Mixson, William C.: Am. J. Obst. & Gynec. 56: 112, 1948.

TRANSPERITONEAL PELVIC LYMPHADENECTOMY FOLLOWING SUPERVOLTAGE IRRADIATION FOR SQUAMOUS-CELL CARCINOMA OF THE CERVIX*

FELIX N. RUTLEDGE, M.D., AND GILBERT H. FLETCHER, M.D.,
HOUSTON, TEXAS

(From the University of Texas M. D. Anderson Hospital and Tumor Institute)

THIS is a report on 100 transperitoneal lymphadenectomies performed on consecutive cases of International Stage III squamous-cell carcinoma of the cervix. These cases were treated by high doses of radiation to the whole pelvis with the use of the 22 Mev betatron and followed by intracavitary radium therapy. This radium dose was proportionately decreased in comparison with previous conventional methods of treatment. The present study is concerned with the irradiation and surgical technique, treatment morbidity, gross anatomic and histologic findings.

The potential therapeutic value of an additional lymphadenectomy following high dose whole pelvis irradiation cannot be ascertained until sufficient time has elapsed for follow-up. For the same reason the delayed complications of this modified form of treatment will also have to be reported at a later date.

Frequency of Pelvic Node Involvement

This project was undertaken to evaluate the effectiveness of irradiation in destroying metastatic squamous-cell carcinoma in regional node areas, that is, the obturator, hypogastric, and external iliac nodes, which can be covered by an external radiation technique. Only inconclusive data can be found on this subject in the literature. Kottmeier[4] has supplied evidence that such sterilization of metastatic cancer on the pelvic wall nodes can be accomplished, by performing a biopsy on such nodes prior to radiation therapy and then, years later, examining the pelvis to find that there was no evidence of disease. There is no valid information as to the incidence of such an achievement in a large homogeneous group. Taussig's[9] and Morton's[6, 7] series of lymphadenectomies in cases of carcinoma of the cervix, treated with radium and with or without external irradiation in addition, are indicative that radiation can be effective in sterilizing metastatic nodes, but the series were not sufficiently controlled for definite conclusions as to the incidence of positive nodes before and after radiotherapy.

*Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

There is no series of consecutive International Stage III squamous-cell carcinomas of the cervix which have been submitted to laparotomy for exploration or for surgical treatment. Therefore a comparison of our incidence of positive pelvic wall nodes has to be made with known data for Stage I, Stage II, and some selected Stage III cases, and a combination of these stages. Such data have been collected by Navratil[8] (Table I).

TABLE I. INCIDENCE OF LYMPH NODE INVOLVEMENT BY STAGES
SURGICAL FINDINGS COLLECTED BY NAVRATIL[8]

STAGE	NO. OF CASES	% INVOLVEMENT
I	383	11.24 ± 1.61
II	395	23.10 ± 2.12
III	232	43.50 ± 3.26

The relative frequency of involvement of the obturator, hypogastric, external iliac, and common iliac nodes has been well studied, although there are obviously some discrepancies between the various authors in the manner in which the various node areas are labeled. Otherwise, there is no explanation for the differences in relative incidence of involvement between these series.

Theoretical Considerations in Irradiation of the Pelvic Nodes

The dose of radiation received by the various node areas from radium therapy has been carefully studied by Kottmeier,[5] Walstam,[10] and Fletcher,[2] by measurements at the time of retroperitoneal lymphadenectomies while the radium is in situ. These studies have demonstrated that the amount of irradiation is quite variable from node area to node area, because of the fact that the inverse-square law produces very rapid changes in dosage in short-range radium therapy. In the Manchester technique, for instance, when the vault of the vagina is very distensible, the obturator or principal node may receive up to 2,000 r. The hypogastric and the external iliac nodes receive approximately one half of that dose and the lower common iliac nodes about one third of the dose. When the vagina is either shortened or made less distensible, by old age or by disease, the radium is lower in the pelvis and the contribution to the obturator node area is, at most, 1,000 r, with proportionate decrease in other node areas.

The variability of dosage and the impossibility of knowing the dose in each individual case, unless direct measurements could be performed while the radium is in situ, render impossible the correlation of dose level with the histologic findings on nodes removed by lymphadenectomy weeks or months following the irradiation therapy. In the classical technique of radium and external irradiation, the contribution to the node area from the external irradiation can be accurately calculated, but the dose is too small to be cancerocidal per se and the contribution from the radium therapy constitutes most of the total dose to the nodes.

Supervoltage roentgen radiation, with the use of 2 Mev equipment, cobalt^{60} therapy unit, or higher voltage equipment such as betatron or linear

accelerator, makes possible high dose irradiation of the whole pelvis. The en bloc irradiation of the whole pelvis, including sufficient margins laterally to cover the external iliac, and upward to cover the hypogastric nodes, at the level of the sacroiliac joints, allows correlation between dose level and the incidence of metastatic involvement of those areas.

The geometric arrangement of two parallel opposing anterior and posterior portals with either a 2 Mev machine or cobalt^{60} teletherapy unit has the disadvantage of producing a high subcutaneous and muscular dose which can result at a later date in crippling fibrosis. Rotation therapy has not been used in the present study because, as shown in Fig. 1, there is a change in dosage rate of approximately 25 per cent in the shell where the node areas are located.

The geometric arrangement of two parallel opposing anteroposterior and two lateral portals (Fig. 1) with a 22 Mev betatron effects homogeneous irradiation of the whole pelvis en bloc, including a margin around it, with no more than 5 per cent variability in dose. With this technique one has, therefore, a known dosimetry. The dose of irradiation to the nodes is known with accuracy.

Based on the experience acquired with combined irradiation and surgery in the treatment of squamous-cell carcinoma of the head and neck, the optimum interval between irradiation therapy and transperitoneal pelvic lymphadenectomy has been set at 3 months. This is sufficient for full histologic changes of irradiation to develop, and yet the fibrosis is not too extensive to prevent complete dissection. Furthermore, longer delay may result in regrowth and extension of viable metastatic cancer. It takes 2 to 3 months for tumor cells to disappear entirely or to disintegrate to the extent that there is no doubt that they are no longer viable. This has been shown in cases of carcinoma of the head and neck region in which 6,000 r has been given over a period of 5 to 6 weeks, followed by radical neck dissection.

Material

The material is limited to cases of squamous-cell carcinoma of intact uteri. The stump carcinomas were excluded because of added uncertainty in the staging of the disease and the even greater paucity of data in the literature on the incidence of lymph node metastases. This institution is a state cancer hospital with a very small percentage of full-paying patients. The ethnic distribution of the material during this time interval is shown in Table II.

TABLE II. ETHNIC DISTRIBUTION

GROUP	NO. OF CASES
White	166
Negro	72
Latin-American	31
Total	269

The high percentage of cases of advanced disease seen during the period of time from April, 1955, to November, 1956, can be noted in Table III.

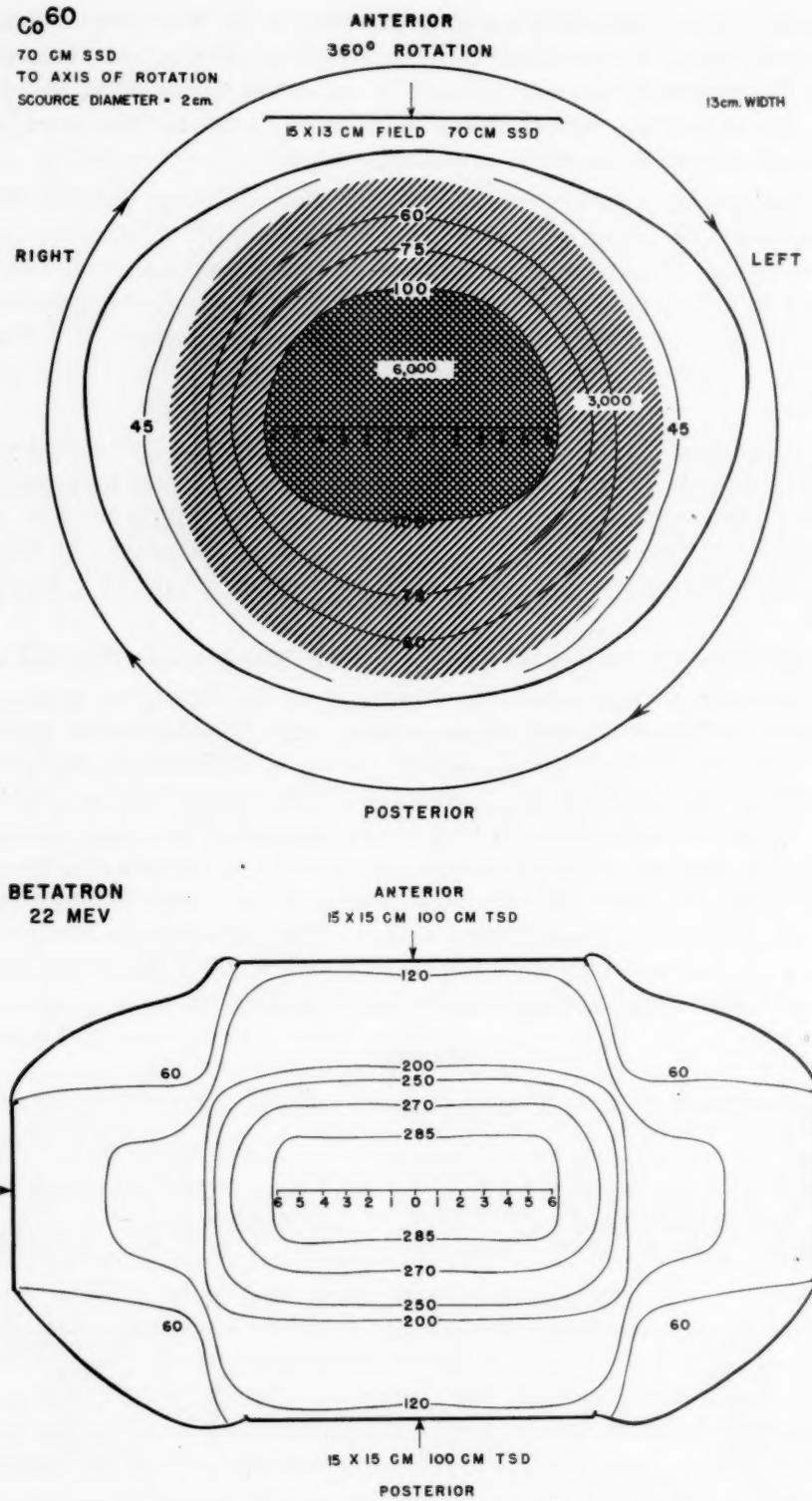


Fig. 1.—The cobalt[60] rotation distribution shows a fall-off of 25 per cent in the zone 5 to 8 cm. from the center of the pelvis where the node areas are located. In the 22 Mev betatron four portal arrangement, the change is only 5 per cent.

TABLE III. DISTRIBUTION ACCORDING TO STAGE OF DISEASE

STAGE	NO. OF CASES
I	38
II	85
III	134
IV	12
Total	269

In 23 cases of Stage III squamous-cell carcinoma of the cervix, a lymphadenectomy was not performed because the patients were considered poor surgical risks. In 11 cases the patients refused operation. The ages of the remaining 100 patients are shown in Table IV and their weights in Table V.

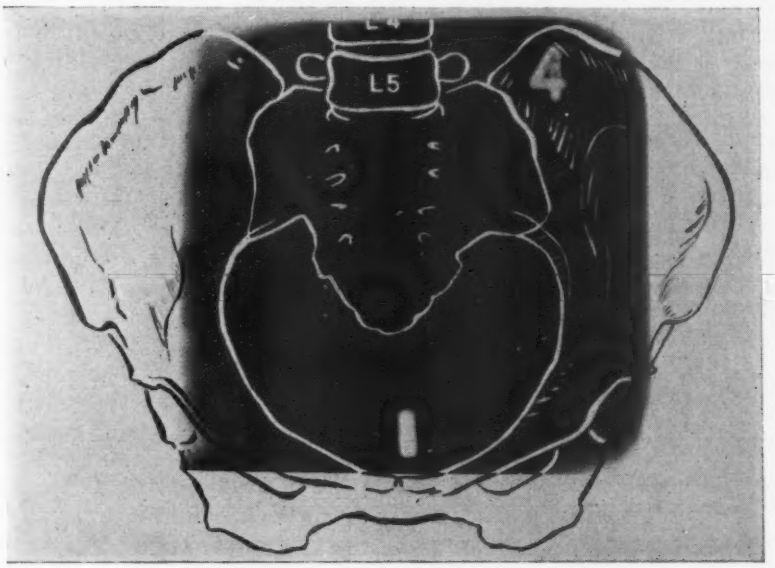


Fig. 2.—Positioning film taken on the 22 Mev betatron. The tip of the lead plug is against the lowest palpable vaginal disease. In this ideal case, part of L_5 is seen.

Irradiation Technique With 22 Mev Betatron

The geometrical arrangement with the 22 Mev betatron consists of four portals: one anterior portal 15 by 15 cm., one posterior portal 15 by 15 cm., two lateral portals 15 cm. high and 9 cm. wide. A plastic rod is introduced into the vagina with its leaded tip against the lowest part of the palpable disease and positioning films are taken with the betatron itself (Fig. 2). The lead plug is used to check coverage of the vaginal disease. The pelvic bony structures are sufficiently clear to identify the anatomic parts that are included within the irradiated area. After adjustments have been made to cover the extent of the vaginal disease adequately, treatment is carried out from day to day with the use of simple mechanical devices which assure satisfactory duplication of each treatment. Unless there is disease very low in the vagina, the entire length of the sacroiliac joint and ideally part of the fifth lumbar vertebra are seen in localization films. This means that the obturator nodes (also called the principal node), the hypogastric, and the external iliac nodes are included. The common iliac nodes are at the margin of the irradiated field with no assurance of their coverage.

In the average case, a total tumor dose of 6,000 r is delivered to the whole pelvis in 6 weeks. At the completion of this treatment, in the more favorable cases of Stage III carcinoma of the cervix, additional radium therapy is given, by means of either a tandem alone or a tandem and colpostats. The dose ranges from 3,000 to 5,000 mg. hr. In the more advanced Stage III cases, that is, in the "frozen pelvis" or nearly frozen pelvis, the total dose can be increased up to 7,000 or 8,000 r over a period of 7 or 8 weeks, respectively; in some of these cases, a greatly reduced amount of intracavitary radium therapy has been added.

Because of the great variability of distance from the radium source to the pelvic wall nodes and the fact that in most Stage III cases the vault of the vagina is not distensible, the maximum dose to the obturator nodes is around 500 to 700 r and the dose to the hypogastric, external iliac, and common iliac nodes from 300 to 500 r. This contribution from the radium is therefore less than 10 per cent of the total dose received. The known dosimetry to the node areas, accurate within 10 per cent, can be correlated with gross anatomic and histologic findings at operation.

TABLE IV. AGES OF PATIENTS WITH STAGE III CARCINOMA

(AGE) YEARS	NO. OF CASES
25 to 30	1
30 to 35	8
35 to 40	14
40 to 45	16
45 to 50	14
50 to 55	15
55 to 60	10
60 to 65	7
65 to 70	12
70 +	3

TABLE V. WEIGHTS OF PATIENTS WITH STAGE III CARCINOMA

WEIGHT (POUNDS)	NO. OF CASES
Less than 100	6
100 to 150	44
150 to 175	32
175 to 200	12
200 to 225	6

Surgical Technique

In a previous series of 75 extraperitoneal lymphadenectomies we felt that the dissection and exposure of the presacral area and the node-bearing tissue in the region of the bifurcation of the aorta were restricted by the lower oblique incision and the retroperitoneal approach. The midline or low transverse incision and transperitoneal approach proved to be superior for exposure and access to the upper abdomen for exploration, which added to the completeness of the information of the metastatic pattern in each case. This preliminary search above the pelvis was routine, but a pelvic node dissection was done regardless of the findings.

The retroperitoneal space is entered by dividing the round ligament about 1 inch from its exit through the internal inguinal ring; the peritoneum is incised upward to the level of the ureter, crossing the common iliac vessels. The ovarian vessels are stripped back from the overlying peritoneum, cleaned of loose fibrofatty tissue, and ligated as close as possible to the cecum on the right and the sigmoid on the left without detaching the vessels from these

structures. Isolation and ligation of these vessels high over the pelvic brim facilitates exposure of the common iliac nodes and reduces the chance of tearing the ovarian vein by retraction. The peritoneal incision is then extended downward from the round ligament to the pubic ramus. The lateral flap of peritoneum is lifted by bluntly pushing off the attached fatty tissue. The medial peritoneal flap with the attached ureter is likewise retracted medially by blunt dissection from the pelvic wall structures.

There is a cleavage plane vertical to the course of the internal iliac artery which can be extended along the lateral side of the superior vesical artery and the bladder to the pubic ramus. Care should be taken to stay lateral to the superior vesical artery, for on this side no significant bleeding will be encountered before the bottom of the obturator fossa is reached.

The nodes can be removed in three main specimen blocks. The largest includes the external iliac, hypogastric, and obturator nodes. For this study these nodes were sent to the pathologists as a separate specimen, but aside from the large and consistent obturator node, which is easily identified, it is difficult to separate them accurately. Above the internal iliac vessels the node-bearing tissue splits to follow each side of the common iliac vessels. The dissection becomes more difficult, for the vessels are less mobile and some of the deeper nodes lie beneath the internal iliac vein and between its divisions. Dissection first on one side and then the other may be necessary to extract the node from between the perforating branches of the internal iliac vein. The common iliac node lies laterally and superiorly, the sacral nodes medially and inferiorly. The latter nodes were found to be quite variable in size. The sacral nodes were the least likely to be removed en bloc and except for the region of the bifurcation of the vena cava very few nodes were found, and none were positive for metastatic carcinoma.

The lower end of the operation is the easiest and safest part and this is done first. Troublesome venous bleeding and problems of exposure are more likely in the common iliac and aortic bifurcation area, which is reserved for the end of the dissection, for blood staining of the operative field is best delayed as long as possible. Venous bleeding that develops can usually best be controlled by direct pressure from a gauze pack. If this does not completely stop the bleeding, the flow will be reduced and the source more easily identified and clamped.

Removal of the nodes starts at the inguinal ligament. The proximal 1 or 2 inches of the inferior segment of the epigastric, circumflex iliac, and obturator vessels are cleaned down to their origins. The dissection proceeds downward past the obturator foramen to the bottom of the paravesical and obturator fossa spaces. The dissection is then directed upward to the aortic bifurcation.

Retraction and dissection about the perforating divisions of the internal iliac vein should be done very cautiously. Bleeding from a torn venous branch may be quite profuse. Dissection of the arteries is simplest. Except for variability in the origin of the obturator artery, their course is consistent and they can tolerate retraction and stripping. Silver clips are used extensively for small bleeding points, which reduces the number of ligatures required. Small vessels perforating the pelvic wall and those supplying the nodal tissue are easily controlled with this method. Postoperative roentgenograms of the pelvis show concentration of these clips at the two ends of the dissection area, which indicates that most of the blood supply to the nodal tissue arises from the region of the inguinal ligament or above the common iliac bifurcation. Very few vascular branches are encountered from the large vessels between these points.

Findings at Operation

Scar tissue of varying degrees was usually seen about the pelvic wall structures, yet in only 3 cases was this fibrosis so extreme that the outline of the large vessels could not be safely followed in sharp dissection. Often this fibrosis stopped at the middle of the common iliac artery, which corresponded approximately to the upper limits of the irradiated field.

An estimation of this fibrosis was made at the time of operation and is recorded by the degree of severity in Table VI. Gross identification of the positive nodes was fairly accurate. They were harder and more adherent, while enlarged negative nodes were usually not so adherent. The greatest error in diagnosis was made on the enlarged but microscopically negative nodes.

TABLE VI. FIBROSIS ENCOUNTERED ABOUT PELVIC WALL STRUCTURES AT OPERATION

DEGREE	NO. OF CASES	
	RIGHT	LEFT
0	8	10
1 plus	40	38
2 plus	21	25
3 plus	21	18
4 plus	10	9

Surgical Complications

In 2 cases it was necessary to ligate one common iliac vein to control bleeding where a branch had torn too close to the wall to be tied. A laceration caused by excessive traction of the common iliac artery at its bifurcation was repaired; no ill effect developed from the repair. In none of the cases did persistent arteriospasm develop. There was good wound healing in all except one case, in which evisceration occurred; this wound healed uneventfully after secondary closure. Some edema of the lower extremities was seen in most of the patients following lymphadenectomy. In some of the cases the edema was severe enough to warrant the use of some elastic support to compress the legs. This edema disappeared within 6 to 8 months.

TABLE VII. INCIDENCE, SIZE, AND TIME OF ONSET OF LYMPHOCELES

	NO.	%
Incidence.—		
Bilateral	21	
Unilateral	10	
	31	
Size.—		
Small	21	
Medium	4	
Large	6	
	31	
Interval Following Operation.—		
1 to 4 weeks	10	32
5 to 8 weeks	12	39
9 to 12 weeks	5	15
3 to 12 months	4	13
	31	

An unanticipated complication of this procedure has been an encysted accumulation of fluid in the dissected area along the pelvic walls. Data pertaining to this complication are summarized in Table VII.

Edema of the mons pubis and upper labia was also noted occasionally, especially in cases where the transverse abdominal incision was used. This edema was more transient than that of the lower extremities.

Pathologic Findings in Lymph Nodes

The surgical specimen was divided into four or more masses. The nodes of the external iliac, obturator, common iliac, hypogastric, and sacral areas were separated for pathologic study. Each node was bisected and a microscopic section made from each half. We believe two sections through each node would be adequate for study; however, to check this opinion, in Cases 1 through 10 and 50 through 60 all the paraffin blocks were serially sectioned and a slide was prepared from every fifth section through the node. In these 20 cases one node was found positive that was not detected by the method of two microscopic sections per node.

In the review of the microscopic changes in the nodes, the findings from nodes inside and those outside the irradiation field were recorded separately. This was done because lymphadenectomy dissection extended above the upper margin of the irradiation field, the upper common iliac and periaortic nodes being above the margin of effective irradiation, the periaortic areas receiving essentially no irradiation and the common iliac areas very little.

For study, the nodes which showed metastatic viable squamous-cell carcinoma can be divided into those that were irradiated and those that were not. The cases with positive nodes are shown in Table VIII.

TABLE VIII. LOCATION OF LYMPH NODES CONTAINING VIABLE METASTATIC SQUAMOUS CARCINOMA

POSITIVE NODES	NO. OF CASES
Only within irradiated field	5
Only outside irradiated field	8
Both inside and outside irradiated field	9

In 2 instances some irradiation effect on the carcinoma cells was shown in positive nodes within the irradiated field. This change was limited to part of the node. Even when the irradiation damage to the tumor cells was severe, other areas of the same or different nodes from the same pelvis contained obviously actively growing squamous-cell carcinoma. These nodes in which the cancer cells were incompletely destroyed were counted as positive.

The nodes within the irradiated field which did not show viable metastatic carcinoma were further studied. Nodes that showed advanced necrosis and fibrosis were studied for residual evidence of destroyed metastatic squamous carcinoma. Although the evidence was meager, after multiple sections in some cases it was possible to identify fragments of dead (ghost cells) squamous carcinoma. There were 4 such cases (Figs. 3, 4, and 5).

Other cases showed the same advanced changes but lacked demonstrable (ghost cells) evidence that metastatic squamous carcinoma had ever been present. These were listed as suspicious of destroyed carcinoma on the direct evidence afforded by the fibrotic and necrotic changes in the nodes. There were 4 such cases (Fig. 6).. There was a third group of nodes that showed fibrosis, calcification, and granulomatous reaction in which the etiology was even more uncertain. This third group of nodes was eliminated from the study.

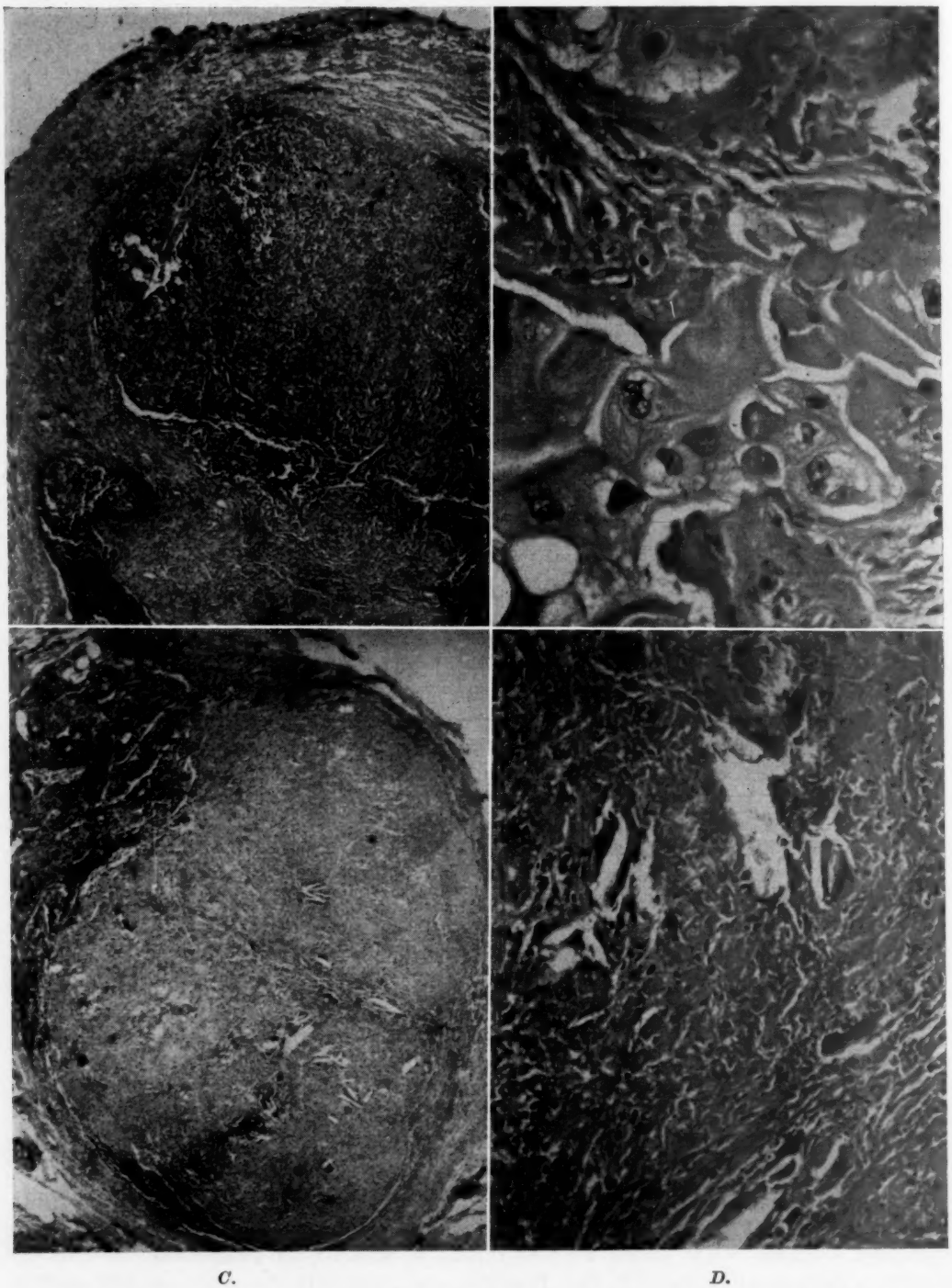


Fig. 3.—Case 1. ***A,*** **Periaortic node (outside the field of effective irradiation) showing viable metastatic squamous-cell carcinoma without any visible irradiation effect.** ***B,*** **Upper common iliac node (margin of the field of effective irradiation) with viable metastatic carcinoma showing irradiation effect.** ***C,*** **Obturator node (within the field of effective irradiation) showing necrosis and granulomatous replacement of the entire node. This node probably contained metastatic squamous-cell carcinoma which was destroyed by radiation.** ***D,*** **Higher magnification of** ***C.***

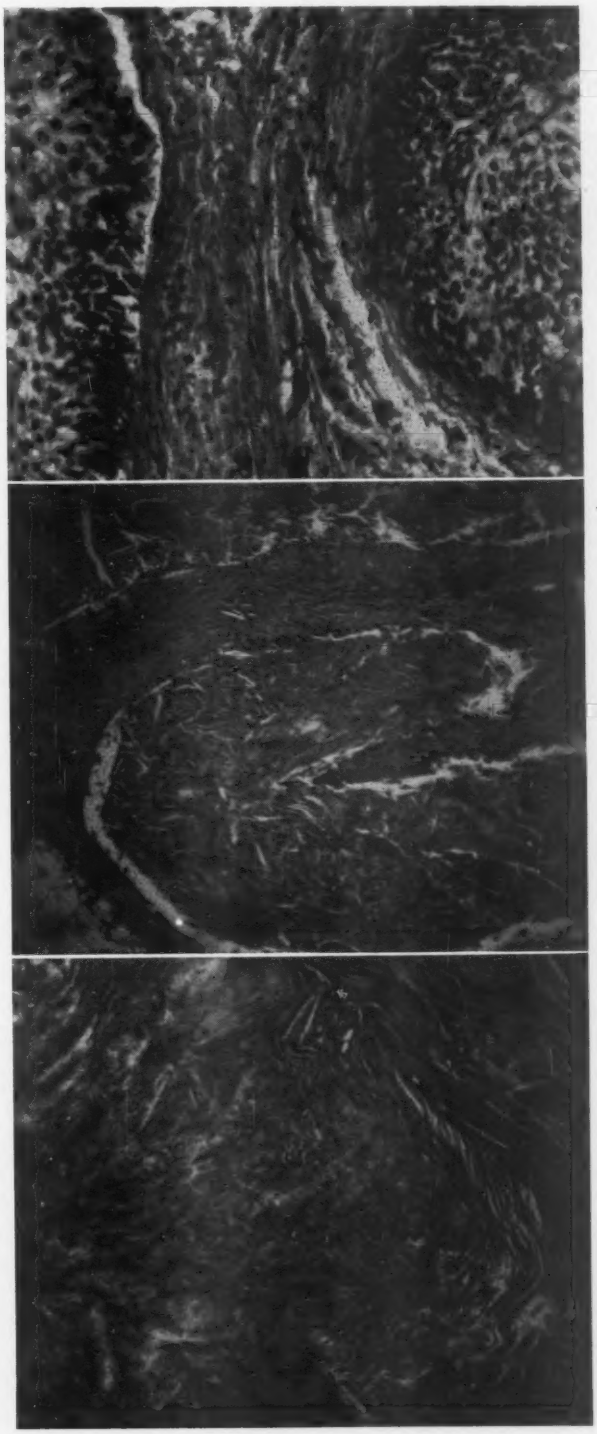


Fig. 4.—Case 2. *A*, Viable metastatic squamous-cell carcinoma in periaortic nodes without visible radiation effect. *B*, Obturator node of the same case showing complete replacement by necrosis and fibrosis with fragments of destroyed carcinoma. *C*, Higher power of an obturator node.

The pelvic nodes in noncarcinoma cases without irradiation therapy occasionally show focal necrosis and granulomatous reaction. Therefore,

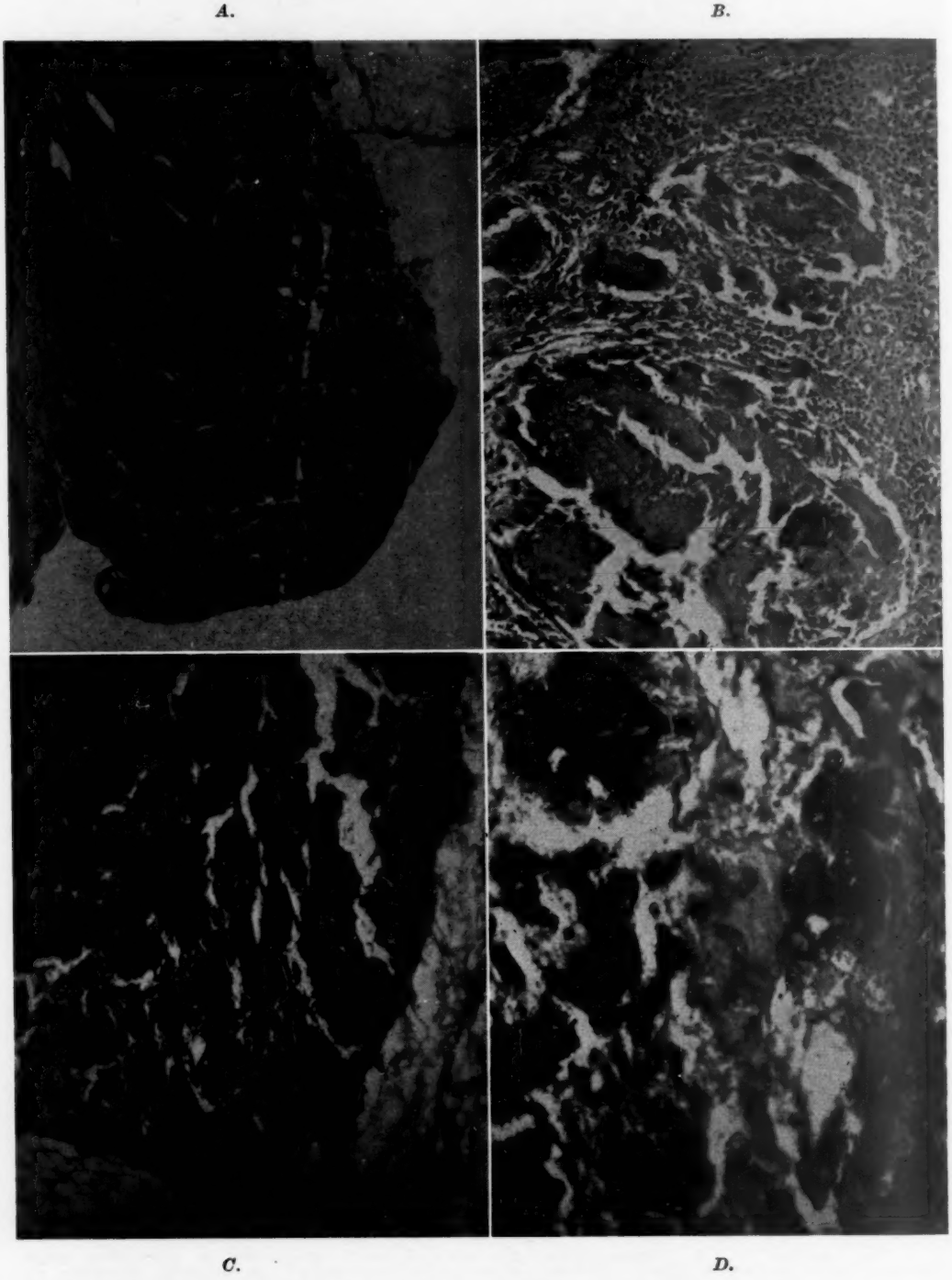


Fig. 5.—Lymph node changes suggesting destruction of carcinoma cells.

Case 3. *A*, Pelvic lymph node replaced by necrosis and inflammatory reaction. *B*, Same slide under higher magnification.

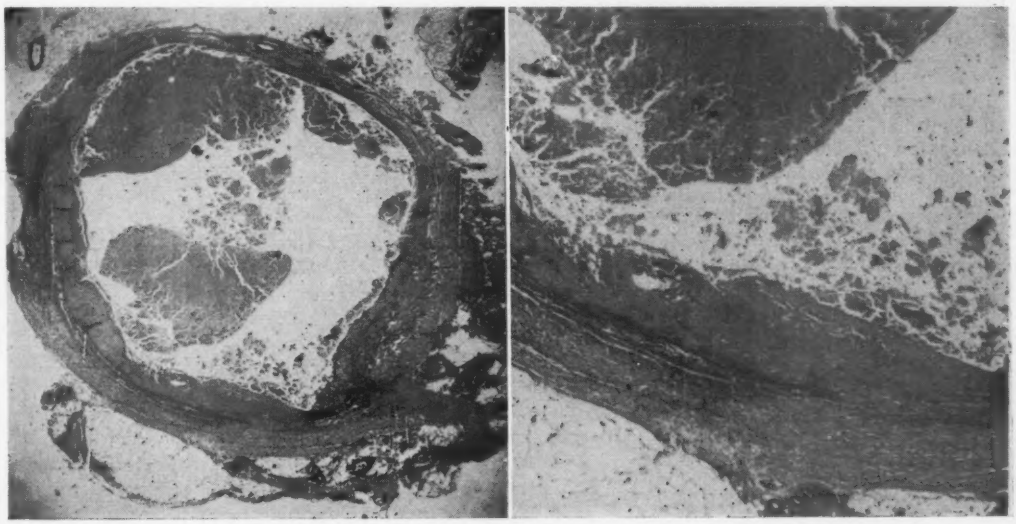
Case 4. *A*, Pelvic lymph node showing destruction and calcium deposition. *B*, Same slide under higher magnification with "ghost cells" of destroyed metastatic carcinoma.

use of these changes as indirect evidence of carcinoma destruction may not be justified or valid.

Irradiation changes in the negative pelvic nodes and surrounding tissues were generally those of atrophy and replacement with scar tissue, adipose tissue, and calcification. These atrophic changes varied from loss of lymphocytic germinal centers and lymphoid depletion within the node to final replacement by connective tissue. Such changes not only varied from those in individual cases which received the same dose, but also within individual cases.

Comment

To evaluate the effects of supervoltage irradiation on metastatic squamous-cell carcinoma we chose Stage III disease. It is in this advanced stage that the number of positive nodes should be large and the usual poor prognosis in Stage III carcinoma of the cervix justifies some experimentation in the therapy. A combination of high dose irradiation and radical node dissection comprises such an experiment. Whether this is therapy which can be tolerated by the patient will have to wait a longer observation period. We had some serious complications in the early part of the study so that this combination is not yet advocated as a form of improved therapy.



A. *B.*

Fig. 6.—Case 5. Complete destruction of a pelvic node. *A*, Low magnification. *B*, High magnification.

We have not discussed the possible therapeutic value of the lymphadenectomy here. There were no controls in this study for such an evaluation; however, we are presently doing a random series of cases with and without lymphadenectomy. Certain technical experience was gained from this series that is valuable for the future study.

Graham's[3] composite tables show an average positive node incidence of:

International Stage I	15 per cent
International Stage II	27 per cent
International Stage III	66 per cent

In addition, Bonney[1] found a 40 per cent positive node incidence in 500 cases operated on out of 900 cases seen (60 per cent operability). His group consisted of all three stages. An estimate of 50 per cent as the incidence for positive nodes in Stage III disease would be conservative. Our incidence of 22 per cent, including common iliac and periaortic nodes, or 14 per cent for the pelvic wall nodes proper, is statistically very significant.

Summary

In this series of lymphadenectomies in 100 consecutive cases of Stage III squamous-cell carcinoma of the cervix that were treated by high doses of radiation given to the whole pelvis, the gross anatomic and histologic findings indicate that high dose whole pelvic irradiation is effective in destroying metastatic squamous-cell carcinoma of the cervix in nodes on the pelvic wall proper. There has been at least a 50 per cent reduction in the incidence of positive nodes.

More intensive series and longer follow-up time will be necessary to determine whether there are changes in the salvage rate. This is radical therapy and adjustments in treatment technique may also be necessary if complications develop with a longer follow-up period.

References

1. Bonney, V.: J. Obst. & Gynaec. Brit. Emp. **48**: 421, 1941.
2. Fletcher, G. H., et al.: Radiology **61**: 885, 1953.
3. Graham, John B.: Surg., Gynec. & Obst. **100**: 149, 1955.
4. Kottmeier, H. L.: J. Fac. Radiologists **2**: 312, 1951.
5. Kottmeier, H. L.: Acta Radiol., supp. 116, p. 406, 1954.
6. Morton, D. G.: AM. J. OBST. & GYNEC. **49**: 19, 1945.
7. Morton, D. G.: Am. J. Roentgenol. **59**: 685, 1947.
8. Navratil, E.: In Meigs, J. V., editor: Surgical Treatment of Cancer of the Cervix, New York, 1954, Grune & Stratton, vol. 6, pp. 218-247.
9. Taussig, F. J.: AM. J. OBST. & GYNEC. **45**: 733, 1943.
10. Walstam, R.: Acta Radiol. **42**: 237, 1943.

ADENOCARCINOMA OF THE UTERINE FUNDUS*

W. O. Johnson, M.D., and Douglas M. Haynes, M.D.,
Louisville, Ky.

(From the Departments of Obstetrics and Gynecology of the University of Louisville School of Medicine, the Kentucky Baptist Hospital, and the Louisville General Hospital)

ALTHOUGH carcinoma of the cervix remains the major problem in gynecologic cancer, endometrial cancer is gaining importance as the life span of its potential victims increases. This lesion is usually signalized by the dramatic symptom of postmenopausal bleeding. Further, a definitive diagnosis can readily be made by the simple expedient of uterine curettage. The prognosis, therefore, ought to be relatively favorable. Published reports have indeed shown a 5 year survival rate which varies from 53 to 89 per cent.

Variables in both diagnosis and treatment make the comparison of different published series problematical even when the reports are from treatment centers. This confusion is multiplied when the patients are treated by a large number of physicians using many different methods. Nevertheless, data from a series of the latter type may be of interest in pointing out deficiencies, as well as indicating the kind of results that may be expected in these circumstances.

Material

The cases reported here were treated and followed in Louisville, Kentucky, during the period 1945-1955. The protocols of 138 patients with proved adenocarcinoma of the endometrium from the private service of the Kentucky Baptist Hospital and from the gynecology clinic of the Louisville General Hospital were reviewed. Thirty-five of these were eliminated from the series, either because the patients were lost to follow-up or their charts provided too little information. This study is concerned with the remaining 103 patients. Eighty-three of these were private patients treated by a number of physicians in private practice; the remaining 20 were seen and managed by the staff at Louisville General Hospital.

Follow-up Classification

Table I shows the follow-up classification used in the present study. It should be noted that the first two groups include patients known to be dead, while the following two groups are patients who survived original treatment for previously known carcinoma. Group V comprises patients treated without initial knowledge of the diagnosis. In this group at least part of the therapy

*Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

given was unplanned. A typical example of such a patient would be a woman subjected to hysterectomy on indications other than carcinoma in whose operative specimen an unsuspected endometrial carcinoma was discovered by the pathologist. Several such patients were encountered in this series.

Table I shows that almost as many patients were alive and well 5 years after planned treatment as were known to be dead of cancer (32 and 33, respectively), while 14 patients survived more than 5 years in spite of the fact that at least part of their treatment was not undertaken with the correct diagnosis in mind. The 24 patients in Group III cannot, of course, be finally evaluated at the present time because 5 years has not elapsed since they were treated.

TABLE I. FOLLOW-UP CLASSIFICATION

Group I	Dead of endometrial cancer less than 5 years after original treatment	28 cases
Group II	Dead of endometrial cancer more than 5 years after original treatment	5 cases
Group III	Alive and free from cancer less than 5 years after original treatment	24 cases
Group IV	Alive and free from cancer more than 5 years after original treatment	32 cases
Group V	Alive and free from cancer 5 or more years after unplanned treatment, the diagnosis being initially unsuspected	14 cases
Group VI	Lost to follow-up or inadequately documented (not included in study)	35 cases

Signs and Symptoms

Clinical data which other authors have considered significant are shown in Table II. Vaginal bleeding was the most common symptom (88.3 per cent).

TABLE II. CLINICAL DATA ON 103 PATIENTS

FINDINGS	SURVIVAL GROUP I	II	III	IV	V	TOTAL	%
Vaginal bleeding	24	4	24	26	13	91	88.3
Enlarged uterus	27	5	20	23	13	88	85.4
Parity	16	3	14	17	8	58	56.3
Myomas	11	5	8	8	8	40	38.8
Obesity	7	4	11	11	5	38	36.9
Endometrial polyps	4	2	6	11	8	31	30.1
Hypertension	10	4	3	9	5	31	30.1

The observed enlargements of the uterus were obviously not all directly related to the presence of the endometrial lesion, since 38.8 per cent of the patients had palpable uterine leiomyomas. Obesity, which was frequent, is an obstacle to both diagnosis and therapy. Of interest also is the specific finding of polyps in almost one third of the entire group of patients studied. The majority of these polyps were endometrial rather than cervical, although this differential diagnosis is often difficult.

TABLE III. AGE DISTRIBUTION AND AVERAGE DURATION OF SYMPTOMS

GROUP	NO. OF PATIENTS	AVERAGE AGE	AVERAGE DURATION OF SYMPTOMS
I	28	57.3	1 year, 3 months
II	5	69.5	1.6 months
III	24	56.1	1 year, 4 months
IV	32	56.4	9.8 months
V	14	56.0	3.8 weeks

The age distribution and average duration of symptoms before institution of treatment are summarized in Table III. The average age of the patients

in the 5 groups is shown to be between 56 and 57.3 years for all but the small group of 5 women (Group II) who survived 5 years or more following treatment but ultimately succumbed to metastatic disease. The advanced average age of this group may be without significance as the total number of patients was very small.

Methods of Treatment

A bewildering diversity of therapeutic approaches to this series of patients is demonstrated in Table IV. Most of the women treated by hysterectomy had a total operation with bilateral salpingo-oophorectomy, although there were 5 instances in which the subtotal operation was done.

As others have also indicated, x-ray therapy appears to play a relatively insignificant adjunctive role in the management of this lesion.

TABLE IV. METHODS OF TREATMENT OF 103 PATIENTS

TREATMENT	TOTAL	SURVIVAL	
		NO. ALIVE	PER CENT
Radium + hysterectomy	36	30	83.3
Hysterectomy only	17	16	94.1
Hysterectomy + x-ray	16	10	62.5
Radium + hysterectomy + x-ray	14	5	35.7
Radium + x-ray only	7	4	57.1
Radium only	5	2	40.0
Hysterectomy + radium + x-ray	3	2	66.6
X-ray only	3	0	0.0
Hysterectomy + radium	1	1	100.0
None	1	0	0.0
Total	103	70	67.9

Survival Rates

Also in line with other published data is the gross mortality of 32.1 per cent shown in Table V. This table also shows the 5 year survival in the 79 patients who were followed long enough for evaluation.

TABLE V. GROSS MORTALITY

		NO.	%
Patients known dead of cancer		33	32.1
Died less than 5 years after treatment	28		
Died more than 5 years after treatment	5		
Salvage		70	67.9
		103	100.0
5 year survival in 79 patients			
Patients known dead		33	41.8
5 year salvage		46	58.2
		79	100.0

Comment

This report illustrates the obstacles to the evaluation of cancer patients resulting from inadequate records and incomplete follow-up. Thirty-five women had to be excluded from this study for one of these reasons. Although this drawback has been avoided in several excellently reported series,[1] the profession must make a greater effort to keep adequate records on all patients, and to secure adequate long-term follow-up.

In any disease with the disastrous sequelae of cancer, it is vital to educate the public to consult the physician at the earliest possible moment. The physician himself, however, must bear some of the blame for delay in treating these women. It is ironic to note that in this study the only patients with average duration of symptoms of less than one month were those in whom the diagnosis of endometrial carcinoma was *not* made by the attending physician until after treatment for some other condition had been instituted. Not only must physician lag in instituting treatment be curbed, but a higher index of suspicion of endometrial cancer should be developed so that the unplanned treatment of initially unsuspected lesions can be cut to a minimum.

Few would dispute that the diagnosis of endometrial carcinoma would be made more often if all instances of postmenopausal bleeding were promptly and routinely investigated by dilatation and curettage of the uterus. Ninety-one of 103 women in this series exhibited vaginal bleeding, and, since the average age of all the patients was 59 years, the postmenopausal resumption of vaginal bleeding was by far the most helpful clinical finding leading to the establishment of a diagnosis of cancer.

Many authors[2] have commented on the coexistence of endometrial carcinoma with obesity (36.9 per cent in this series), endometrial polyps (30.1 per cent) and hypertension (30.1 per cent). As previously pointed out, the difficulties of therapy are increased by obesity, since this interferes with the technical procedures of radium insertion and surgical attack. Our incidence of polyps (30.1 per cent) is higher than that reported by others; for example, Scheffey, Thudium and Farell[3] found polyps in only 7.8 per cent of 127 patients and, of these, only 10 per cent demonstrated malignant changes. Nevertheless, the possibility of so-called malignant degeneration at the base of an endometrial polyp is a definite one. The relationship between hypertension and endometrial cancer is obscure: it may possibly be a factor of the age group involved.

Some differences of opinion are expressed in published reports regarding the treatment of choice in endometrial carcinoma. The extensive 5 year survival studies reported by Kottmeier[4] suggest that comparable results may be obtained by surgery with postoperative irradiation, preoperative intracavitary radium followed by hysterectomy, and primary radium therapy with hysterectomy in failures. With few exceptions, the experience of American gynecologists favors the combination of intracavitary radium (average dose 4,000 to 6,000 mg. hr. in 1 to 3 applications), followed by total hysterectomy and bilateral salpingo-oophorectomy in 6 to 8 weeks. Peightal and Crawford[5] stated that with the standard use of this method, the 5 year survival rate should be about 64 per cent for all patients with endometrial carcinoma.

Total hysterectomy and bilateral salpingo-oophorectomy alone may produce good results in early cases, as was the case in the present study, but it seems wiser to employ the combined therapy in all patients with lesions which have not spread beyond the uterus. In addition to the possibility that prior intracavitary radium application may reduce the chance of spillage implantation at operation, shrinkage of the bulky and friable lesion lessens the technical problems involved. We believe that the preferred management of most cases of endometrial carcinoma should consist of accepted dosage of intracavitary radium followed in 6 to 8 weeks by total hysterectomy and bilateral salpingo-oophorectomy.

No radical operations of the Wertheim type were attempted in this series, and most authors agree with Corscaden and Tovell's[6] assertion that the radical

operation is not indicated in endometrial cancer since, when positive pelvic lymph nodes have been found, their removal has not resulted in improvement in salvage rates.

In this, as in other reports the use of x-ray therapy was restricted to advanced cases, and is considered as possibly palliative but certainly not curative.

Summary and Conclusions

1. Clinical data are presented on 103 patients treated in Louisville, Kentucky, for adenocarcinoma of the uterine fundus during the decade 1945 to 1955.

2. The importance of early diagnosis and adequate follow-up and documentation is stressed.

3. The survival rate in 79 women followed 5 years or more was 58.2 per cent.

4. The treatment of choice is intracavitary radium application followed in 6 to 8 weeks by total hysterectomy and bilateral salpingo-oophorectomy.

References

1. Javert, C. T., and Douglas, R. G.: Am. J. Roentgenol. **75**: 508, 1956.
2. Peel, J. H.: Am. J. Obst. & Gynec. **71**: 718, 1956.
3. Scheffey, L. C., Thudium, W. J., and Farell, D. M.: Am. J. Obst. & Gynec. **46**: 786, 1943.
4. Kottmeier, H. L.: Gynaecologia **138**: 287, 1954.
5. Peightal, T. C., and Crawford, D. B., Jr.: Obst. & Gynec. **5**: 438, 1955.
6. Corscaden, J. A., and Tovell, H. M. M.: Am. J. Obst. & Gynec. **68**: 737, 1954.

A COMPARATIVE STUDY OF THE DISAPPEARANCE OF RADIOACTIVE SODIUM FROM HUMAN UTERINE MUSCLE IN NORMAL AND ABNORMAL PREGNANCY*†

EDMUND B. WEIS, JR., M.D., PAUL D. BRUNS, M.D., AND E. STEWART TAYLOR, M.D., DENVER, COLO.

(From the Department of Obstetrics and Gynecology, University of Colorado School of Medicine)

THE pioneering work of several British investigators[1-4] on placental and myometrial circulation has provided a new approach to the study of normal and abnormal physiology in the human gravid uterus. Their methods consist of injecting a tracer amount of radioactive sodium into the intervillous space and/or the myometrium and recording the time for one half of the radioactivity to disappear. Their experimental results show that there is a delay in the disappearance of radioactive sodium from the injected sites in cases of toxemia as compared to normal controls. They interpret these data to indicate reduced placental and myometrial circulation in the toxemias of pregnancy.

With the use of this same tracer technique, preliminary studies[5, 6] performed in this department indicated that premature labor was associated with three rather constant factors: reduced urinary excretion of steroid metabolites, increased uterine contractility, and delayed disappearance of radioactive sodium from the myometrium. These changes were observed most frequently in complicated prematurity, but were found also in patients who were delivered prematurely without apparent cause. This study was designed to establish the pattern of disappearance of radioactive sodium from the myometrium during the last half of normal pregnancy and to compare these data with those from abnormal pregnancy, both full term and premature.

Method

The method used was essentially identical with that described by Kety.[7] The radioactive isotope employed was $Na^{22}Cl$ with a half life of 2.6 years, and the usual dose was 5 μc in 0.2 ml. of normal saline. This isotope emits both positive beta particles and gamma rays. Counting was done with an end-window Geiger tube and rate meter. The site of injection was approximately 2 inches below and 2 inches to the left of the umbilicus. A No. 22 gauge needle

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†Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.

was inserted through the anterior abdominal wall into the myometrium and aspiration carried out to make certain that neither a vessel nor the amniotic sac had been entered. The radioactive isotope was injected with a tuberculin syringe and the needle quickly withdrawn. Without delay the Geiger tube was placed over the site of injection of the radioactive sodium. During the counting period, care was taken to maintain the original geometric positions. Counting was recorded every 15 seconds. At the end of the counting period, the tube was placed in the same position on the right side of the abdomen and control readings were made for background irradiation. The values obtained in this manner were corrected for the constantly increasing blood level of radioactivity by the formula suggested by Morris and associates.[2] The corrected values were plotted against time on semilogarithmic graph paper, and a slope determined. From this slope, the time taken for one half of the radioactivity to disappear from the myometrium was calculated and termed "T/2" or time to half value in minutes.

Material

A total of 127 pregnant patients from the Obstetrical and Gynecological Department of the Colorado General Hospital were included in this study (Table I). Sixty-four of these parturients had normal gestations and were delivered at or near term. Twenty-five patients were delivered prematurely. Twelve of these had complicated pregnancies and 13 were delivered prematurely without apparent cause. Twenty-one patients had toxemia of pregnancy, 6 of whom had premature deliveries. Each of 7 patients with poor obstetrical histories was given 60 mg. of natural estrogens* daily by mouth for one month during late pregnancy. Radioactive sodium studies were done before and after estrogen administration. In 10 other patients the technique was unsatisfactory and the results were excluded.

TABLE I. TOTAL NUMBER OF PATIENTS STUDIED

	NO. OF PATIENTS	NO. OF DETERMINATIONS	HALF VALUE IN MINUTES	STANDARD DEVIATION
Normal full-term pregnancy	64	64	4.00	1.87
Premature delivery				
Uncomplicated pregnancy	13	21	3.51	1.60
Complicated pregnancy	12	12	7.71	2.51
Patients with poor obstetrical history	7			
Before estrogen therapy		6	6.17	2.55
After 4 weeks estrogen		6	6.46	2.63
Toxemia of pregnancy	21	21	8.20	3.42
Technically unsatisfactory	10	10	----	----

Results

Normal Full-Term Pregnancy.—From the twenty-second to the thirty-eighth week of pregnancy the mean disappearance time for 51 patients was 3.5 minutes. When labor occurred, membranes ruptured prematurely, or term was passed, the mean time for 13 patients increased to 6.1 minutes. There was no statistically significant difference between these two categories. Hence, when these 64 normal cases were grouped together, the disappearance time for radioactive sodium averaged 4.0 minutes (Fig. 1).

*Premarin, 15 mg. capsules, supplied by Ayerst Laboratories, New York, N. Y.

TABLE II. DATA ON 25 PATIENTS WHO WERE DELIVERED PREMATURELY

CASE	AGE	RACE OR NATIONALITY	PARITY	PREVIOUS COMPLICATIONS	WEEK OF TEST	WEEK OF DELIVERY	WEIGHT (GRAMS)	HALF VALUE		PRESENT COMPLICATION
								MINUTES	SECONDS	
Single Determinations.—										
1	21	Negro	i	Pre-eclampsia	34	35	2,400	4	15	Hypertension
3	23	Negro	iii	Habitual abortion	26	26	1,150	6	15	Labor
5	22	White	ii	Pre-eclampsia	36	37	2,500	5	30	Labor, toxemia
10	20	Spanish-American	ii	None	34	34	2,120	2	15	Premature rupture
12	33	Negro	iii	3 premature deliveries	40	40	2,350	1	15	Premature rupture
14	21	Spanish-American	ii	Pre-eclampsia	36	36	2,250	5	15	Hypertension
25	31	Negro	iii	2 premature deliveries	38	39	2,400	4	30	Premature rupture
33	29	White	v	2 premature deliveries	36	36	2,370	7	45	Premature labor
36	21	White	iii	2 premature deliveries	34	34	2,020	7	30	Premature labor
38	32	Spanish-American	iii	Pre-eclampsia	34	34	2,200	12	15	Bleeding, toxemia
41	22	Negro	i	Hyperthyroidism	32	32	1,920	11	45	Abruptio placentae
52	17	White	0	None	38	38	2,400	3	15	Premature rupture
58	23	White	0	None	30	34	2,130	5	00	None
80	33	Negro	vii	Hypertension	34	38	2,470	3	15	None
86	22	White	0	None	34	34	1,990	2	00	None
95	28	Negro	vii	Hypertension	24	24	480	9	00	Bleeding
104	20	White	ii	Hypertension	30	33	1,800	8	30	Twins
108	27	White	0	None	34	35	2,150	6	00	Toxemia
128	20	Spanish-American	0	Pyelitis	34	37	2,220	4	00	None
130	42	Negro	v	None	34	39	2,500	7	15	Toxemia
Serial Determinations.—										
A	31	Negro	iii	1 premature delivery	28			4	30	None
					32			5	45	None
					36	40	2,420	6	45	None
B	22	White	0	None	30			1	30	None
					34	36	2,430	8	45	Pyelitis
C	21	Spanish-American	iv	3 premature deliveries	22			1	45	None
					26			4	30	None
					32	34	2,340	2	15	None
D	26	Spanish-American	ii	2 premature deliveries	30			5	45	None
					34	35	2,300	3	00	None
E	25	White	ii	2 premature deliveries	22			2	30	None
					26			2	15	None
					34			5	45	None
					38	40	2,480	2	00	None

Premature Delivery.—Twenty-five patients who were delivered prematurely had serial or single determinations (Table II). Serial studies were done on 5 of these patients at 4 week intervals during late pregnancy. All determinations, except one performed on a patient who developed acute pyelitis, were within the normal range. In uncomplicated spontaneous premature labor with or without rupture of the membranes, the mean disappearance time was 3.5 minutes. This figure was obtained from a total of 21 determinations on 13 patients. When premature labor was complicated by twins, toxemia, bleeding, or infection this half-value time increased to 7.7 minutes. In general, the more serious the complication the greater the disappearance time (Fig. 2).

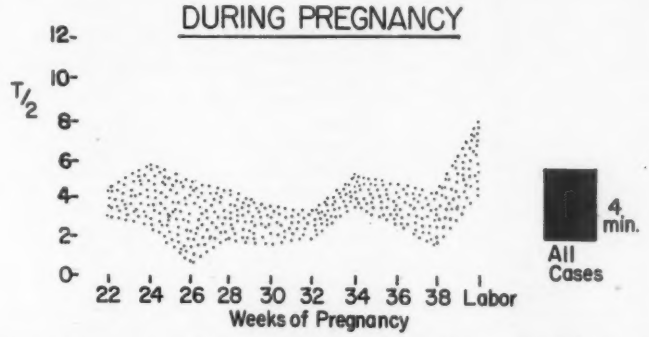

Fig. 1.—Disappearance of radioactive sodium from the myometrium was determined at weekly intervals throughout the last half of normal pregnancy. The average time to half value in 64 patients was 4 minutes.

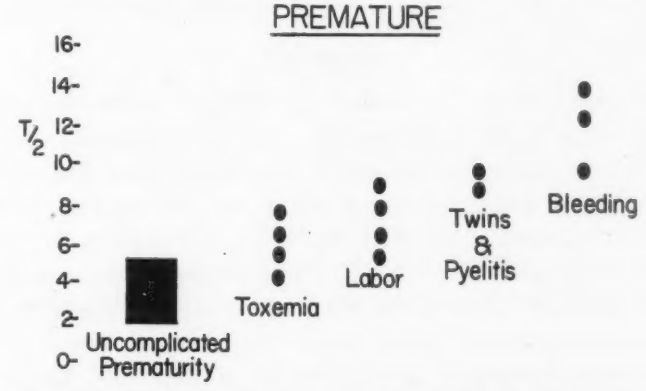

Fig. 2.—Disappearance of radioactive sodium from the myometrium in patients with complications of pregnancy showed a prolonged time to half values. In general, the more serious the complication, the more delayed was the disappearance of radioactive sodium from the myometrium.

Toxemia of Pregnancy.—Twenty-one patients developed the usual signs and symptoms of toxemia with an elevation in blood pressure of 140/90 or above (Table III). Their mean disappearance time was 8.2 minutes or double the normal value. No correlation was found between the degree of hypertension, type of toxemia, or duration of symptoms. The increased disappearance time preceded the onset of toxemic symptoms in 2 patients and the onset of labor in half of the patients studied (Fig. 3).

Patients With Poor Obstetrical Histories.—Seven patients were selected for special study and therapy because of a history of repeated premature deliveries or habitual abortions. An initial determination was done after the twentieth week of pregnancy on each patient. All of them were given 60 mg. of natural

estrogens daily by mouth, for one month and then a repeat isotope study was done. Pretreatment and posttreatment values were near 6 minutes. Premarin therapy in the large amounts used did not alter the disappearance time in patients with a poor obstetrical background.

TABLE III. DATA ON 21 PATIENTS WITH TOXEMIA OF PREGNANCY

CASE	WEEK OF TEST	WEEK OF DELIVERY	CLASSIFICATION	INFANT'S WEIGHT (GRAMS)	HALF VALUE	
					MINUTES	SECONDS
5	36	36	Pre-eclampsia	2,500	5	30
1	34	35	Hypertension	2,400	4	15
14	36	36	Hypertension	2,250	5	15
38	34	34	Hypertension	2,200	12	15
108	38	39	Pre-eclampsia	2,150	6	00
130	34	39	Pre-eclampsia	2,500	7	15
13	38	38	Hypertension R	3,400	5	45
23	38	38	Hypertension	3,100	5	00
24	40	40	Hypertension	3,450	10	15
31	32	40	Unclassified	2,700	6	15
45	38	38	Unclassified	3,970	10	00
47	38	40	Pre-eclampsia	2,800	7	30
54	40	40	Pre-eclampsia R	2,700	4	30
71	40	40	Pre-eclampsia	3,250	6	45
103	42	43	Pre-eclampsia	3,650	9	30
101	36	40	Pre-eclampsia	2,960	12	45
105	38	40	Pre-eclampsia	2,740	8	30
114	36	Term	Hypertension	Term	7	15
94	38	38	Unclassified	2,530	18	00
125	24	39	Hypertension	3,100	6	75
157	34	Term	Hypertension	Term	13	00

Comment

The results obtained in the normal and toxemic patients in this study show close correlation with those published by other investigators. The values found in the parturients who were delivered prematurely were somewhat unexpected for they differed from the values obtained in the preliminary study.[6] Furthermore, in 5 uncomplicated cases with delivery before term, in which *serial* determinations were done at 4 week intervals during mid-pregnancy, no change in myometrial clearance time could be demonstrated. These findings are contrary to our original concept, based upon experimental observations, that a defect in myometrial circulation might be the underlying mechanism in spontaneous premature labor of undetermined cause. These data also showed that an increased disappearance time of radioactive sodium was associated with most complications of pregnancy regardless of whether the patient was delivered prematurely or at term. Furthermore, the vast majority of the complications of pregnancy were vascular in nature, namely, pre-eclampsia, chronic hypertention, or renal disease.

In 13 additional cases of premature delivery which are not reported in this study, simultaneous determinations of urinary steroids, uterine motility, and disappearance times were done. The same trend of reduced excretion of estrogen and pregnanediol, uterine hypermotility, and increased myometrial clearance times was evident, but not statistically significant when compared to the data from the normal control cases.

Kety has established both theoretically and experimentally a direct and constant relationship between tissue clearance of radioactive sodium and tissue circulation. It may be stated that observations which have been made upon the human pregnant uterus following intramyometrial injection of radioactive sodium have been based upon Kety's classic experiment. Hence, previous investigators have spoken in terms of myometrial circulation time and uterine blood flow. If their assumptions are correct, then the observations herein reported also show a diminished uterine blood flow in complicated pregnancy, as compared to that in normal gestation. Although such a hypothesis is very attractive, interpretation of results of all such experiments in terms of volumetric or velocity blood flow is still a matter of conjecture. Many aspects of this technique must yet be evaluated. They will form the subject of a subsequent report.

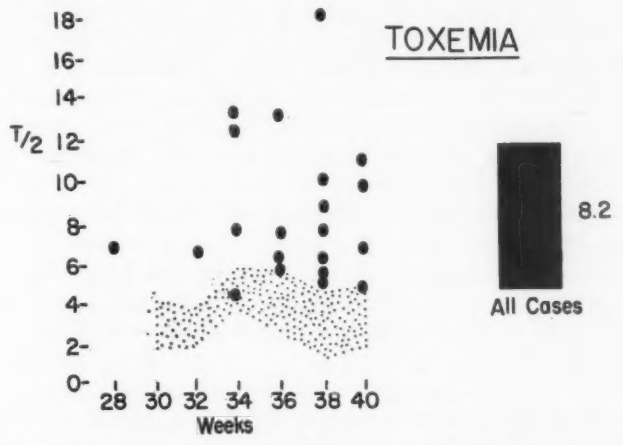

Fig. 3.—The mean disappearance time of radioactive sodium from the myometrium in 21 patients with toxemia was 8.2 minutes, or double the normal value. In 11 patients, the prolonged disappearance time preceded the onset of labor by 1 to 8 weeks.

Conclusions

1. Disappearance of radioactive sodium from the myometrium or "time to half value" from the twentieth to the fortieth week of normal pregnancy averages 3.5 to 4.0 minutes.

2. In an uncomplicated pregnancy that terminates prematurely, disappearance time from the twentieth to the thirty-fourth week averages 3.5 minutes to half value.

3. When pregnancy of any gestational length is complicated by toxemia, bleeding, infection, or twins, the myometrial clearance time averages 8.0 minutes.

4. Exactly what factors and mechanisms in terms of uterine circulation are reflected by the intramyometrial injection of radioactive sodium needs further elucidation.

References

1. Browne, J. C. M., and Veall, N.: J. Obst. & Gynaec. Brit. Emp. 60: 142, 1953.
2. Morris, N., Osborn, S. B., and Wright, H. P.: Lancet 1: 323, 1955.

3. Johnson, T., and Clayton, C. G.: Brit. M. J. 1: 312, 1957.
4. Moore, P. T., and Myerscough, P. R.: J. Obst. & Gynaec. Brit. Emp. 64: 207, 1957.
5. Taylor, E. S., Bruns, P. D., Anker, R. M., and Drose, V. E.: AM. J. OBST. & GYNEC. 70: 894, 1955.
6. Bruns, P. D., Taylor, E. S., Anker, R. M., and Drose, V. E.: AM. J. OBST. & GYNEC. 73: 579, 1957.
7. Kety, S. S.: Am. Heart J. 38: 321, 1949.

Discussion

DR. ROY G. HOLLY, Omaha, Neb.—The authors are to be commended for the enormous amount of work which has gone into the investigation. They are exploring the important problem of uterine blood flow with an investigative tool which offers the possibility of solving this and other medical unknowns. The isotope method has an accuracy beyond the limits of former methods using gadgets, dyes, gases, and so forth. Radioactive sodium permits measurement of plasma volume with more accuracy than is obtained when the Evans blue dye is used. The isotope of phosphorus is used for red-cell-mass determination. With the iron isotope Fe^{59}, it is possible to study the absorption, storage, utilization, and excretion of iron. Our whole concept of iron metabolism has been altered with the introduction and application of the isotope method of investigation. Radioactive iodine has been adopted as a routine laboratory tool in the study of thyroid function. Carbon 14-labeled steroids have opened up the field of study of steroid metabolism. These are but a few of the areas being explored by means of tracer amounts of isotopes. The isotope method has a precision not obtainable by other means. Now, a few well-controlled experiments can often replace great numbers of individual tests performed with cruder techniques and with greater accuracy.

Yet, for all the accuracy inherent in measurement with isotopes, it is our interpretation of the data which may be the deficient link in our search for scientific knowledge. An experiment as complex as the one presented suggests this possibility.

I sense a certain reluctance on the part of our essayist to say that he is measuring uterine blood flow or even myometrial circulation. In this complex problem the sodium ion has been used and accordingly many variables peculiar to the metabolism of this element are introduced. It has been injected into an extravascular space. What is the total sodium space and what is the sodium concentration in the intravascular and extravascular compartments? These factors must certainly affect the behavior of the sodium ion. What is the diffusion rate for the sodium ion? Is it necessary to consider arteriovenous shunts? In other words, for this problem the T/2 value could be the function of any number of variables and not necessarily a measure of circulation. I would like to ask Dr. Bruns if he has information on the sodium space and concentration.

May I suggest a possible explanation for the prolonged T/2 values in patients with toxemia? Kety's original formulation on which this investigation is based assumed that the sodium space was constant. Would not the greatly enlarged sodium space known to be present in toxemia explain the prolonged clearance time even if circulation and blood flow times were the same?

One final point which I would like to raise is relative to the radiation hazard imposed by this type of investigation. We have an investigational tool of infinite value yet it may create so great a hazard as to exclude its use. Stewart and Webb recently reported twice the incidence of leukemia in children who had received irradiation in utero from ordinary x-ray pelvimetry. Recent studies at Johns Hopkins as reported by the National Academy of Sciences suggests 25 r as the safe total maximum irradiation up to the age of 30. Kety estimated the exposure for infants in utero as 2.5 r when 5 μc of Na^{24} was used, an isotope with a shorter half life than Na^{22}. I would like to ask Dr. Bruns if an estimate of total irradiation was made for Na^{22}, especially in patients who received serial study.

ABRUPTIO PLACENTAE AND HYPOFIBRINOGENEMIA*†

JACK A. PRITCHARD, M.D., DALLAS, TEXAS

(From the Department of Obstetrics and Gynecology of the University of Texas Southwestern Medical School)

FROM the many published reports dealing with abruptio placentae in the past several years it is apparent that there is considerable difference of opinion concerning many aspects of this syndrome. The precise mechanism by which placental separation is produced is not clear; the pathway by which hypofibrinogenemia develops remains to be proved; the proposed methods of management of a patient with abruptio placentae very considerably.

This report deals with the problem of alterations in the hemostatic mechanism in abruptio placentae. Analyses of clinical observations coupled with laboratory studies will be utilized in an attempt to answer the following questions: (1) At what rate does hypofibrinogenemia usually develop as the result of abruptio placentae? (2) Does uncorrected hypofibrinogenemia always result in excessive blood loss following delivery of the products of conception? (3) At what rates are the alterations in the hemostatic mechanism spontaneously corrected? (4) What is the role of blood transfusions in the treatment of hypofibrinogenemia? (5) When should specific fibrinogen replacement therapy be instituted?

Material and Methods

At the time of admission of every patient to the labor-delivery area, blood was drawn and 4 to 5 ml. was placed in a clean, dry test tube and allowed to clot. Therefore, for any case a reference clot was available which by simple inspection would establish the presence or absence of significant hypofibrinogenemia when the patient was admitted. This blood was ultimately used for serological tests for syphilis.

When abruptio placentae was suspected, a rapid clot observation test was performed as follows: Stoppered ordinary glass test tubes 13 mm. in diameter which contained approximately 0.1 ml. (2 drops) of topical thrombin solution (1,000 N.I.H. units per milliliter) were kept for this purpose in the freezing compartment of a refrigerator in the area. About 1 ml. of freshly drawn blood was placed in the tube. Normally, a firm clot will appear almost immediately because of the conversion of fibrinogen to fibrin by thrombin. With hypofibrinogenemia of clinical importance there may be no visible clot or the

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clot may at first inspection appear normal. In the latter instance if in a few minutes the tube is tapped against a firm surface, the clot will retract to a small ball from which most of the red cells will be extruded and the liquid phase will exceed the clot in volume. This test, first suggested by Page,[1] rapidly indicates the presence or absence of significant hypofibrinogenemia and therefore is clinically most useful.

Whenever the clot observation test suggested the presence of hypofibrinogenemia, plasma was obtained for a quantitative fibrinogen determination. In some of the cases of hypofibrinogenemia direct platelet counts and measurements of plasma fibrinolytic activity were carried out. All methods used have been described in a previous report.[2]

The amounts of blood lost from the genital tract were calculated by measuring at delivery all blood which could be readily collected; the additional blood lost was estimated by visual inspection and added to the measured loss.

Therapy with whole blood was deliberately limited to amounts judged to be necessary to combat the signs and symptoms of shock irrespective of the hematocrit or hemoglobin concentration. Fibrinogen was given only when uncontrollable hemorrhage had occurred, until later in the study when it had become evident that massive bleeding could be anticipated at the time of abdominal surgery if the hypofibrinogenemia had not been corrected.

Significant hypofibrinogenemia associated with placental separation was encountered in 11 subjects during a period of 16 months. The lowest plasma fibrinogen concentration detected in each case ranged from less than 5 mg. to 125 mg. per 100 ml. Vaginal delivery was utilized in 6 subjects, none of whom received fibrinogen. Delivery via the abdominal route was carried out in 5; 3 received 4 Gm. and one received 3 Gm. of fibrinogen, while fibrinogen was not given to one. Blood transfusions were used in all cases; the volumes of whole blood administered ranged from 500 ml. to 3,000 ml., and averaged 1,400 ml.

In 2 of the cases where therapy had been limited to 1 unit of blood, on the day after delivery the plasma volume was measured with Evans blue dye so that the absolute increase in circulating fibrinogen could be determined during the first 24 hours after the uterus was emptied.

To determine the concentration of fibrinogen in donor blood after collection in acid-citrate-dextrose (ACD) solution and to measure the effect of storage on its fibrinogen concentration, 30 specimens of such blood were assayed. In 10 instances the plasma fibrinogen level was determined immediately after the blood was collected. In 5 instances the blood had been stored from one to 7 days, in 8 from 8 to 14 days, and in 7 from 14 to 21 days prior to assay.

An attempt was made to determine the approximate incidence of homologous serum jaundice following therapy with fibrinogen. Each member of the Central Association of Obstetricians and Gynecologists was asked the number of cases in which he had used fibrinogen and the number of cases of homologous serum jaundice which followed.

Case Summaries

A. Vaginal Delivery.—

CASE 1.—B. B., gravida v, para ii, 35 weeks pregnant, was awakened at 3:00 A.M. by lower abdominal pain soon followed by moderate vaginal bleeding. She was admitted to the obstetric service at 8:40 A.M. at which time the uterus was hard and fetal heart tones were absent. A clot observation test showed an abnormally small clot.

Moderate bleeding from the vagina continued. At 11:20 A.M. the membranes were ruptured artificially. At this time the patient was having intermittent abdominal pain

which was thought to be due to labor; the cervix was 4 cm. dilated. The plasma fibrinogen level was 63 mg. per 100 ml.; the hematocrit was 23. Abnormal fibrinolytic activity was not demonstrated.

The patient was delivered spontaneously at 12:00 noon. The recently dead fetus was followed by the placenta and 1,000 ml. of blood and blood clots. The fibrinogen level at this time was 67 mg. per 100 ml.

A continuous intravenous infusion of Pitocin and massage of the fundus were started immediately following delivery and the uterus remained firmly contracted. Subsequent blood loss was slight.

At 3:20 P.M. the fibrinogen level was 99 mg. per 100 ml. and the hematocrit was 18. The patient was not actively bleeding nor was she in shock but, because of the extensive blood loss prior to and at the time of delivery and the marked anemia, 500 ml. of blood was given. Twenty-four hours after delivery the fibrinogen concentration was 280 mg. per 100 ml. (Fig. 1). The patient recovered.

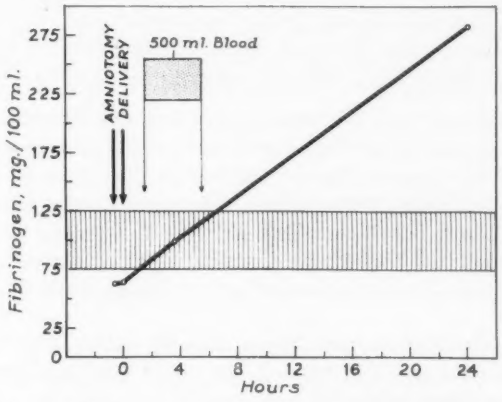

Fig. 1.—Case 1. Vaginal delivery; hypofibrinogenemia was present but fibrinogen therapy was not necessary to control bleeding.

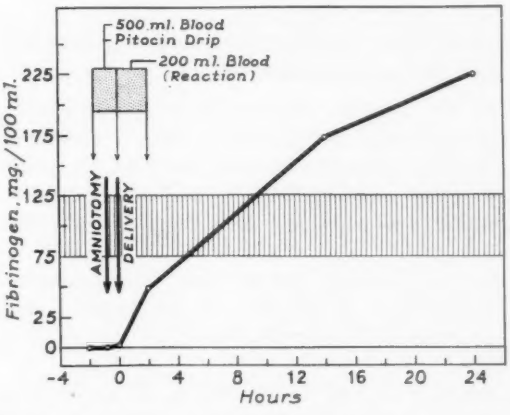

Fig. 2.—Case 2. Vaginal delivery; afibrinogenemia was present but was not specifically treated.

CASE 2.—I. W., gravida vi, para v, 38 weeks pregnant, was admitted to the labor-delivery area at 4:30 P.M., 3 hours after the sudden onset of abominal pain and 2½ hours after the onset of marked vaginal bleeding. Blood was obtained for immediate type and cross-match, a clot observation test, and a quantitative fibrinogen determination. No clot formed. The fibrinogen level was less than 5 mg. per 100 ml.

Ringer's-lactate solution and 30 minutes later 500 ml. of blood were started. At this time the membranes were ruptured artificially through a cervix dilated to 3 cm. and 1 ml. of Pitocin was added to the Ringer's-lactate solution.

Moderate bleeding from the vagina continued and blood oozed from all sites of venipuncture whenever there was manipulation within their vicinity.

At 6:35 P.M. spontaneous delivery occurred. A small stillborn fetus was followed immediately by the placenta and 1,000 ml. of liquid and clotted blood. The plasma fibrinogen level was less than 10 mg. per 100 ml. at this time.

Following delivery the Pitocin infusion was continued and fundal massage was instituted. The uterus contracted firmly and blood loss from the vagina was not excessive. Any manipulation within the vicinity of the sites of the venipunctures, however, continued to result in their bleeding freely. For instance, when the blood pressure cuff was inflated, brisk bleeding from recent puncture sites in the arm promptly developed. This blood did not clot.

Two hours following delivery urticaria was noted after 200 ml. of the second unit of blood had been administered, so it was discontinued. The plasma fibrinogen level was 48 mg. per 100 ml. The uterus remained firmly contracted and vaginal bleeding did not exceed normal limits. Fourteen and 24 hours after delivery the fibrinogen levels were 172 and 225 mg. per 100 ml., respectively. The patient recovered (Fig. 2).

CASE 3.—S. B., gravida v, para iii, was admitted to the labor-delivery area at 10:30 P.M. She was somewhat disoriented but apparently had noted abdominal pain with moderate vaginal bleeding starting 30 hours before admission. At the time of admission a clot observation test showed a clot which was smaller than normal; the plasma fibrinogen level was 132 mg. per 100 ml. Abnormal plasma fibrinolytic activity was not demonstrated.

Whole blood was started and at 12:20 A.M. vaginal examination revealed the cervix to be 3 cm. dilated. An amniotomy was performed and an intravenous infusion of Pitocin was started.

At 3:20 A.M. spontaneous delivery of a fetus showing evidence of beginning maceration occurred, followed by the placenta and 950 ml. of liquid and clotted blood. The plasma fibrinogen level was 125 mg. per 100 ml.

The Pitocin infusion was continued and fundal massage was started; the uterus remained firmly contracted. Blood loss from the uterus after completion of the delivery was never excessive.

Six and 30 hours after delivery the plasma fibrinogen concentration was 163 and 285 mg. per 100 ml. respectively. The patient recovered.

CASE 4.—A. S., gravida xiv, para iii, who was 26 weeks pregnant, noted sudden rather severe abdominal pain which persisted for several minutes. Fetal movement was not felt after this. At 1:15 P.M., 2¼ hours after the onset of the pain, she was admitted to the labor-delivery area. The blood pressure was 146/100, no vaginal bleeding was noted, fetal heart tones were absent, the membranes were intact, the cervix was dilated to 5 cm., and regular uterine contractions were present.

At 6:30 P.M. the patient was delivered spontaneously of a nonmacerated stillborn infant that weighed 840 grams. At the start of the delivery the intact membranes were ruptured artificially. The placenta and about 700 ml. of clotted and liquid blood promptly followed the fetus.

During the next few minutes another 250 to 300 ml. of blood escaped from the vagina. The uterus remained poorly contracted. A clot observation test revealed a barely visible clot. The plasma fibrinogen concentration at this time was 25 mg. per 100 ml.

Five hundred milliliters of blood was started and the genital tract was explored. Further therapy was limited to fundal massage and an intravenous infusion of Pitocin. The uterus promptly contracted and blood loss was reduced to normal.

The clotted blood drawn at the time of admission to the hospital was examined and contained a large firm clot which entrapped most of the erythrocytes, ruling out clinically significant hypofibrinogenemia at the time of admission 5 hours before delivery.

Two hours after delivery the plasma fibrinogen level was 76 per 100 ml. Sixteen and 24 hours after delivery it was 215 and 245 mg. per 100 ml., respectively. The patient recovered (Fig. 3).

CASE 5.—E. S., gravida v, para iii, 38 weeks pregnant, noted the onset of abdominal pain and vaginal bleeding at 6:00 A.M. At 10:30 A.M. the membranes ruptured spontaneously. Sterile vaginal examination at this time showed moderate vaginal bleeding somewhat in excess of a normal bloody show and the cervix to be 2 cm. dilated. Uterine contractions of moderate intensity were observed.

At 2:30 P.M. a living female infant who survived was delivered spontaneously, followed by 500 ml. of liquid and clotted blood. The placenta was manually removed. Firm dark clots were adherent to about one third of the maternal surface of the placenta. The genital tract when explored by direct vision and palpation was normal. An intravenous infusion of diluted Pitocin was started and the uterus promptly contracted.

A clot observation test just after delivery of the placenta showed an abnormally small clot; the plasma fibrinogen level was 42 mg. per 100 ml. The clotted blood drawn at the time of admission was checked and also revealed an abnormally small clot, indicating that hypofibrinogenemia was present at least 4½ hours before delivery.

Thirty minutes after delivery vaginal bleeding was again excessive and the uterus was atonic; the infusion of Pitocin was found to be infiltrating the subcutaneous tissue. Fundal massage was instituted, the Pitocin solution was restarted intravenously, and 500 ml. of blood was given. Abnormal bleeding promptly ceased.

Two hours after delivery the fibrinogen level was 61 mg. per 100 ml. and 22 hours after delivery it was 220 mg. per 100 ml. The patient recovered.

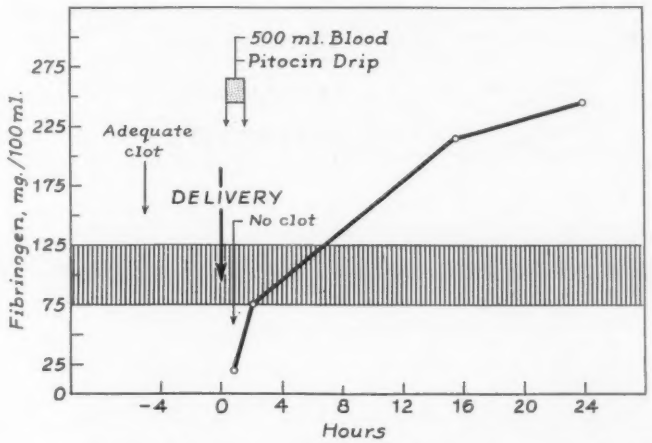

Fig. 3.—Case 4. Vaginal delivery; severe hypofibrinogenemia developed within 5 hours.

CASE 6.—L. L., gravida ii, para i, 32 weeks pregnant, was admitted to the labor-delivery area at midnight. Approximately 36 hours prior to admission she noted persistent abdominal pain with cessation of fetal movements. Heavy vaginal bleeding started 7 hours prior to admission. This was confirmed by a physician who saw her at home.

When admitted to the hospital the blood pressure was 130/90 and the pulse rate 120; the uterus was hard and fetal heart tones were absent. Aqueous fluids were started intravenously and 1,500 ml. of compatible whole blood were requested from the blood bank. The hemoglobin level and hematocrit were 8.0 Gm. and 26, respectively.

At 12:45 A.M. a clot observation test resulted in a small unstable clot. At this time the blood pressure was 130/84 and the pulse rate 100. At 12:50 A.M. spontaneous delivery without anesthesia was accomplished, yielding a stillborn fetus followed by 1,400 ml. of liquid and clotted blood and the placenta.

Two ampules of Methergine was added to the infusion of dextrose in water. The uterus seemed well contracted following this, yet persistent and moderately excessive vaginal bleeding was noted. An examination of the genital tract under general anesthesia was started at 1:25 A.M. At this time the hemoglobin level and hematocrit were 7.0 Gm. and 22 respectively, and the fibrinogen concentration was shown subsequently to be 85 mg. per 100 ml.

With the start of the anesthetic the blood pressure fell to 90/60 and the pulse rate rose to 130. A laceration extending from beside the urethra into the vagina was the primary source of the bleeding. Anesthesia was continued during the repair of this laceration. The patient's condition continued to deteriorate as judged by vital signs. Even though compatible whole blood was in the operating room, unfortunately none was started until 2:15 A.M., at which time the blood pressure could no longer be detected by the anesthetist. The patient was pronounced dead at 2:40 A.M.

An autopsy was performed. Positive findings were limited to extensive intramural and subserosal uterine hemorrhage, slight to moderate hemorrhage beneath most of the pelvic peritoneum, and the vulvovaginal laceration previously described. A careful search of the lungs revealed no histological evidence of either fibrin thromboemboli or particulate matter from amniotic fluid. Death undoubtedly resulted from hypovolemic shock due to hemorrhage without adequate blood replacement therapy.

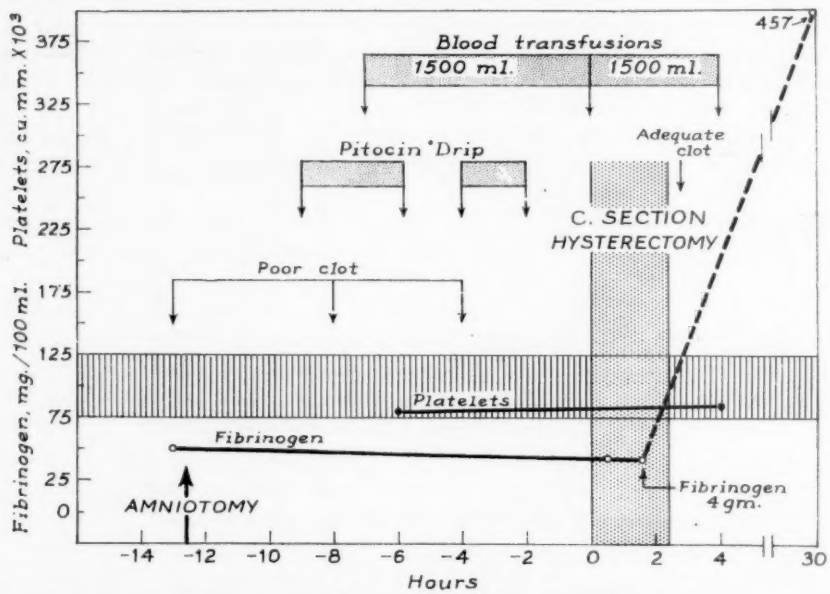

Fig. 4.—Case 7. Cesarean section and hysterectomy; severe hemorrhage was encountered during the operation until fibrinogen was given.

B. Delivered by Laparotomy.—

CASE 7.—N. J., gravida v, para i, 30 weeks pregnant, was admitted at 1:15 P.M. complaining of abdominal pain which had begun 6 hours earlier. There was marked hypertension, edema, and proteinuria. The uterus was hard and fetal heart tones were absent; the cervix was partially effaced but only barely dilated. An amniotomy was done.

Bleeding and clotting times were normal; however, the end point for the clotting time was not sharp because of the small unstable clot which formed. The plasma fibrinogen level was 53 mg. per 100 ml. and the direct platelet count was 84,000 per cubic millimeter.

At 5:15 P.M. an intravenous infusion of diluted Pitocin was started in an attempt to initiate labor. This was continued for a 3 hour and a 2 hour period during the next 7 hours

without progressive dilatation of the cervix. During this time vaginal bleeding persisted at a rate of about 100 ml. per hour.

At 3:20 A.M., 14 hours after admission, following the two attempts to stimulate labor with Pitocin and the administration of 1,500 ml. of blood, a laparotomy was performed. About 1,500 ml. of bloody fluid and blood clots was found free in the peritoneal cavity. Considerable bleeding from all cut surfaces was encountered, so a subtotal hysterectomy was performed, but hemostasis could not be achieved. Four grams of fibrinogen was given intravenously and the bleeding decreased markedly. Blood loss, including that in the uterine cavity and free in the peritoneal cavity, was approximately 3,500 ml. Fifteen hundred milliliters more of blood was given during and after operation. At the end of the procedure the clot observation test revealed an adequate clot; the direct platelet count was 84,000 per cubic millimeter. Thirty hours after delivery the plasma fibrinogen level was 457 mg. per 100 ml.

The patient's postoperative course was complicated by oliguria and azotemia, typical of acute tubular necrosis. She ultimately recovered (Fig. 4).

CASE 8.—E. B., gravida ix, para vi, 38 weeks pregnant, was admitted to the labor-delivery area at 2:00 P.M., one hour after the onset of severe abdominal pain and moderate vaginal bleeding. The uterus was tense and the fetal heart was not definitely heard. The cervix was only partially effaced and was dilated barely enough to allow an amniotomy to be performed. A clot observation test revealed an adequate but somewhat small clot; the plasma fibrinogen level was 196 mg. per 100 ml. at 3:20 P.M.

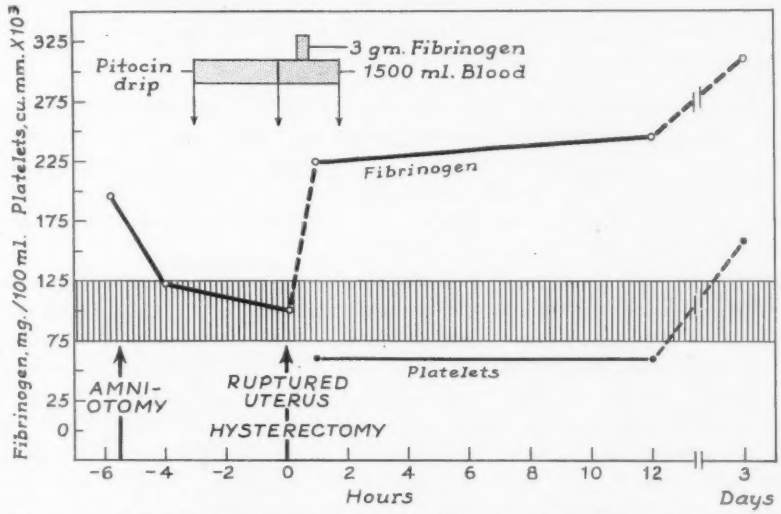

Fig. 5.—Case 8. Ruptured uterus and hysterectomy; extensive hemorrhage from all cut surfaces ceased after fibrinogen therapy.

At 5:30 P.M. the fibrinogen level was 122 mg. per 100 ml. One hour later, in spite of the patient's parity, an infusion of diluted Pitocin was started in an attempt to stimulate labor and dilate the cervix.

Two and one-half hours later the patient stated something tore inside her. Abdominal and vaginal examination showed a ruptured uterus. Laparotomy was immediately performed with whole blood being administered but without fibrinogen therapy. A supracervical hysterectomy was undertaken. There was marked bleeding from all cut surfaces, and from the nose and gums. Bloody fluid was obtained when the airway was aspirated.

The plasma fibrinogen concentration at this time was 100 mg. per 100 ml. After injection of 3 Gm. of fibrinogen intravenously, satisfactory hemostasis was promptly achieved. A total of 1,500 ml. of blood was given.

One hour later the fibrinogen level was 225 mg. per 100 ml. and the direct platelet count was 62,000 per cubic millimeter. Twelve hours later the fibrinogen level was 245 mg. per 100 ml. and the platelet count was 60,000 per cubic millimeter. On the third postpartum day they were 285 mg. and 158,000. The patient recovered (Fig. 5).

CASE 9.—W. D., gravida ii, para i, 32 weeks pregnant, was admitted to the labor-delivery area at 5:30 P.M., 4 hours after the onset of persistent abdominal pain. The uterus was firm and tender; fetal heart sounds were absent; the cervix was only slightly effaced and barely dilated.

The clot observation test showed a very small clot. At 6:30 P.M. the plasma fibrinogen level was 27 mg. per 100 ml.

The patient started to bleed slightly from the vagina. At 8:30 P.M. the cervix was dilated enough to allow an amniotomy to be performed. At 9:30 P.M. an intravenous infusion of Pitocin was started but this resulted in little change in the cervix.

At 10:50 P.M. the plasma fibrinogen level was 48 mg. per 100 ml. An assay for plasma fibrinolytic activity revealed clot lysis to be normal.

Since there was a steady increase in pulse rate, whole blood was started. At 11:10 P.M., because of no progress and continued blood loss, it was decided to deliver the patient by laparotomy. Four grams of fibrinogen was given during the next 40 minutes. Following this the fibrinogen level was 140 mg. per 100 ml.

A cesarean section was performed without incident. The wall of the uterus was extensively infiltrated with blood but following closure and the addition of Pitocin to the intravenous fluids, it remained firmly contracted. A total of 1,000 ml. of blood was given.

Eleven hours after operation the fibrinogen level was 170 mg. per 100 ml.; 24 hours later it was 255 mg. per 100 ml. Recovery was prompt.

CASE 10.—O. L., gravida ix, para viii, 34 weeks pregnant, was admitted to the labor-delivery area at 1:45 A.M. Two hours previously she had noted sudden intense abdominal pain soon followed by heavy vaginal bleeding. Examination showed hypotension, tachycardia, a hard uterus, no fetal heart tones, and brisk vaginal bleeding. The cervix was 2 cm. dilated and no placenta was felt. A clot observation test showed a small clot; the plasma fibrinogen level was 53 mg. per 100 ml.

Whole blood was started, 4 Gm. of fibrinogen was given, and promptly a cesarean section was performed with no difficulty in achieving hemostasis. Blood had extensively infiltrated the wall of the uterus but it contracted well after it was closed. At 3:40 A.M., at the end of the procedure, the fibrinogen level was 153 mg. Six hours later it was 185 and the direct platelet count was 70,000 per cubic millimeter. The next day the plasma fibrinogen level was 334 mg. per 100 ml. but the platelet count was only 69,000 per cubic millimeter. On the second, third, and fourth postoperative days the platelet count rose to 109,000, 176,000 and 184,000 per cubic millimeter, respectively. The patient recovered (Fig. 6).

CASE 11.—A. I., gravida i, para 0, 36 weeks pregnant, awoke with abdominal pain at 1:30 A.M. At 2:45 A.M. a gush of blood from the vagina was noted. When admitted to the hospital at 3:10 A.M. she was hypertensive and the uterus was very firm. Her blood formed a clot of normal size. Amniotomy was performed through a cervix dilated to 2 cm. Fetal heart tones were never definitely heard.

At 4:45 A.M. the plasma fibrinogen concentration was 98 mg. per 100 ml. Abnormal fibrinolytic activity was not demonstrated. Vaginal bleeding persisted. Intravenous Pitocin was tried for 1¼ hours without any demonstrable effect.

At 8:45 A.M. a cesarean section was started with cyclopropane anesthesia. The plasma fibrinogen level was now 30 mg. per 100 ml.; the platelet count was 115,000 per cubic millimeter.

The placenta was completely separated. Blood had infiltrated the uterus and broad ligaments to the serosa. Intravenous Pitocin was started as soon as the uterus was emptied

and the uterus promptly contracted. A continuous ooze of blood was encountered from the cut margins of the abdominal wall during the procedure and for 6 to 7 hours after closure. Vaginal bleeding seemed somewhat excessive but not alarming during this interval.

Three units of blood were administered, 500 mil. during operation and 1,000 ml. in the next 6 hours.

Subsequent fibrinogen and platelet concentrations during the puerperium were as follows: 8 hours, fibrinogen 112 mg.; 26 hours, fibrinogen 270 mg.; 36 hours, fibrinogen 317 Mg. and platelets 106,000; 72 hours, fibrinogen 435 mg. and platelets 145,000. The patient recovered (Fig. 7).

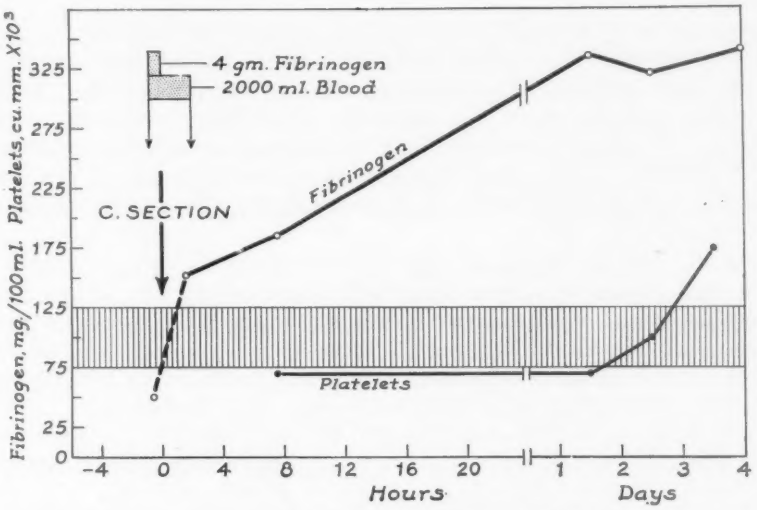

Fig. 6.—Case 10. Cesarean section following fibrinogen administration was performed without excessive bleeding.

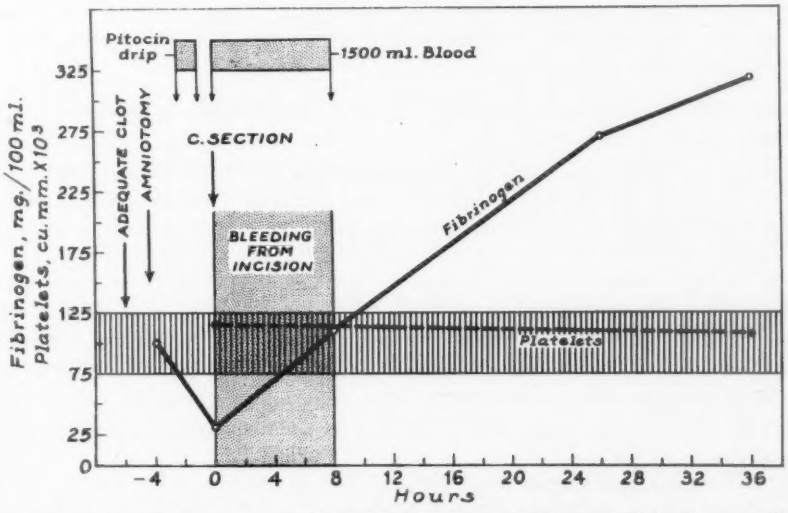

Fig. 7.—Case 11. Delivery by cesarean section was performed without correction of the hypofibrinogenemia.

Analyses of Results

The observations made in these cases of abruptio placentae and in related studies have been utilized in an attempt to answer the questions outlined in the introduction.

Most of the observations and interpretations are not original. Many of them support those previously made by several, but with about equal frequency they conflict directly with the observations and interpretations of others. Due to the voluminous literature which has accumulated concerning this subject no attempt has been made to include complete references to previous investigations. Extensive bibliographies concerning this subject may be found with the reports of Weiner, Reid, and Roby,[3] Jackson and co-workers,[4] and Ratnoff and associates.[5]

1. At what rate does hypofibrinogenemia usually develop as the result of abruptio placentae?

In 8 instances a potentially dangerous degree of hypofibrinogenemia, determined by either the clot observation test, the quantitative measurement of plasma fibrinogen concentration, or both, was present when first looked for at or shortly after admission of the patient to the labor-delivery area. The interval between the onset of symptoms of placental separation and the demonstration of hypofibrinogenemia ranged from 2 to 36 hours. In 6 out of 8 patients symptoms had been present for 6 hours or less; in one the interval was only 2 hours.

In Cases 4, 8, and 11 at least part of the interval during which hypofibrinogenemia developed was demonstrated. In Case 4, 2¼ hours after the onset of abdominal pain, the plasma fibrinogen level, as judged by clot size, was normal, but 5 hours later the plasma fibrinogen level was only 25 mg. per 100 ml. In Case 8 the plasma fibrinogen level was reduced to 196 mg. per 100 ml. 2½ hours after the onset of abdominal pain. Two hours later, in spite of amniotomy, it had fallen to 122 mg. per 100 ml. In Case 11, 5½ hours after a clot of normal size was demonstrated, the plasma fibrinogen level was 30 mg. per 100 ml.

Comment.—These observations again emphasize the necessity of frequent measurements of the level of circulating fibrinogen, either by the clot observation test or by some other simple and rapid method. From 1 hour to no more than 2 hours is recommended as a practicable interval between such observations in cases of abruptio placentae.

2. Does uncorrected hypofibrinogenemia always result in excessive blood loss following delivery of the products of conception?

In 3 instances (Cases 1, 2, and 3) immediately after spontaneous vaginal delivery an intravenous infusion of Pitocin and fundal massage were started. The uterus remained well contracted and, in spite of the hypofibrinogenemia, blood loss from the genital tract was not excessive. In 2 others (Cases 4 and 5), once uterine atony was overcome, hemorrhage from the genital tract ceased even though the fibrinogen deficit persisted. The absence of postpartum hemorrhage seemed quite remarkable in Case 2 in which the plasma fibrinogen level was less than 10 mg. per 100 ml. and rather profuse bleeding developed from all needle puncture sites whenever there was any manipulation within their vicinity, yet blood loss from the genital tract following delivery was not excessive.

In Case 6, following spontaneous delivery, blood loss from the genital tract was in excess of normal even though the uterus seemed to be well contracted. Inspection showed this blood to be escaping predominantly from an extensive periurethral and vaginal laceration rather than from the uterus.

When delivery was accomplished by the abdominal route without previous correction of the deficiency in circulating fibrinogen, extensive and persistent bleeding was encountered in 2 out of 3 cases, even though the degree of hypofibrinogenemia was no greater than in the cases where vaginal delivery was

accomplished. In Cases 7 and 8 all cut surfaces bled extensively. This bleeding was not controlled by hysterectomy. In fact, this procedure only resulted in increased hemorrhage. Correction of the deficit in circulating fibrinogen promptly resulted in the control of the generalized bleeding. In Case 11 persistent oozing of liquid blood from the incision was noted during and after closure but the volume of blood lost was not massive; the uterus had the classic appearance of a Couvelaire uterus but remained contracted after it was emptied. In the cases in which the hypofibrinogenemia was corrected prior to laparotomy (Cases 9 and 10), abnormal bleeding from cut surfaces was not encountered. In both cases the uterus contracted well and postpartum blood loss was not abnormal.

It might be argued that the excessive bleeding in Cases 7 and 8, in which laparotomy was performed prior to fibrinogen therapy, resulted, at least in part, from thrombocytopenia. In Case 10, however, where fibrinogen was given preoperatively, an equal degree of thrombocytopenia was present in the postpartum period, yet blood loss was not excessive. Moreover, in Cases 7 and 8 fibrinogen therapy promptly controlled the hemorrhage while the thrombocytopenia persisted.

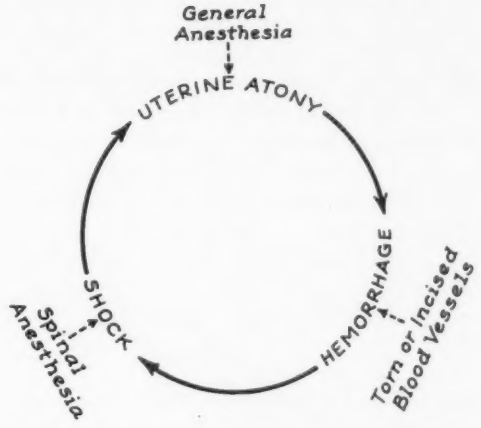

Fig. 8.—Shown are the factors of major importance in the genesis of hemorrhage from the site of placental implantation.

Comment.—Observations in these subjects support the concept that a normal blood coagulation system is not mandatory to achieve hemostasis at the site of placental implantation.[8] Instead, a well-contracted myometrium immediately postpartum is the major factor in effecting hemostasis at this site.

On the other hand, the blood coagulation mechanism must on occasion be of some aid in establishing hemostasis at the site of placental implantation. Several cases have been reported of hypofibrinogenemia in which vaginal delivery was followed by hemorrhage from the uterus, but when the fibrinogen deficit was corrected the hemorrhage was quite promptly controlled. It is plausible that in such cases myometrial tone was submaximal, allowing excessive bleeding, but when adequate clot formation was restored this provided enough aid to achieve hemostasis. It should be emphasized, however, that no amount of fibrinogen will control hemorrhage if the uterus remains atonic. Massive hemorrhage can occur from an atonic uterus even though the hemostatic mechanism is perfectly normal.

It is apparent from the present observations that lacerated or incised blood vessels in the remainder of the genital tract (Case 6) or elsewhere in the body (Cases 7, 8, and 11) do not have a vasoconstrictive mechanism for controlling blood loss comparable in efficiency to the well-contracted myometrium.

If it is elected not to correct the hypofibrinogenemia prior to delivery, it appears mandatory to make every effort to minimize trauma either to the genital tract or elsewhere and to avoid factors which might contribute to uterine atony. Therefore, in the presence of uncorrected hypofibrinogenemia, either light analgesia or nothing rather than general or spinal anesthesia should be used, episiotomy and genital tract lacerations should be avoided, and any degree of shock should be promptly corrected to avoid the possibility of the cycle of events shown in Fig. 8.

3. At what rates are the alterations in the hemostatic mechanism spontaneously corrected?

In 4 cases of quite severe hypofibrinogenemia with vaginal delivery, by purposefully withholding therapy with fibrinogen and giving only a small volume of blood (200 to 500 ml.) after delivery, it was possible to measure the rate at which the fibrinogen deficit was spontaneously corrected. The fibrinogen level at or a few minutes after delivery ranged from less than 10 to 67 mg., and averaged 35 mg. per 100 ml. As shown in Fig. 9, during the next 24 hours the fibrinogen level rose progressively and in roughly linear fashion. At 2, 6, 12, and 24 hours after delivery it averaged 70, 105, 160, and 250 mg. per 100 ml., respectively.

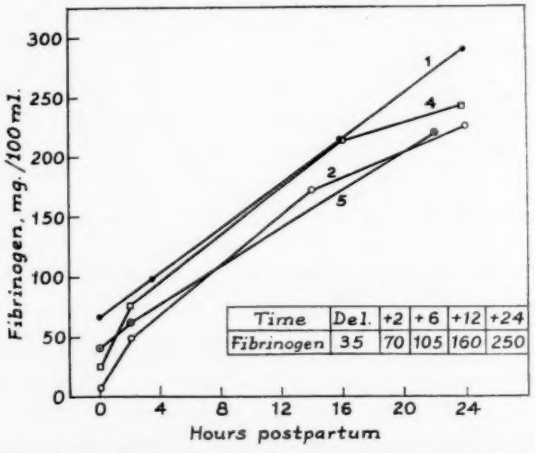

Fig. 9.—Plotted are the fibrinogen levels in Cases 1, 2, 4, and 5 during the first 24 hours following vaginal delivery. Therapy was limited to 200 to 500 ml. of blood during this period.

In 2 of these cases the absolute increase in circulating fibrinogen during this interval was determined. As shown in Table I, more than 5 Gm. of fibrinogen was added to the intravascular compartment as the result of synthesis during the first 24 hours after delivery.

Thrombocytopenia was corrected at a much slower rate than was the hypofibrinogenemia. In Cases 8 and 10 the platelet concentrations rose from a detected low of 60,000 and 70,000, respectively, shortly after delivery to the low normal range of 158,000 and 176,000 per cubic millimeter on the third postpartum day.

TABLE I. INCREASES IN TOTAL CIRCULATING FIBRINOGEN WITHIN 24 HOURS AFTER VAGINAL DELIVERY (THERAPY LIMITED TO 500 ML. OF BLOOD)

	FIBRINOGEN (MG./100 ML.)		PLASMA VOLUME	TOTAL FIBRINOGEN (GM.)		
	INITIAL	FINAL	(ML.)	INITIAL	FINAL	INCREASE
A.S.	25	243	2,680	0.7	6.5	5.8
B.B.	67	280	2,550	1.7	7.1	5.4

Comment.—In the presence of severe hypofibrinogenemia the rate of spontaneous correction is too slow to guarantee protection of the patient from exsanguination during the early puerperium, since 8 to 12 hours usually elapse before the plasma level reaches 150 mg. per 100 ml., a level which will assure adequate clot formation.

Thrombocytopenia, at least of the intensity observed in these patients, does not appear to be a significant factor in the genesis of hemorrhage following delivery, even though the thrombocytopenia is corrected at a much slower rate than is the fibrinogen deficit.

4. What is the role of blood transfusions in the treatment of hypofibrinogenemia?

That blood transfusions can readily correct hypovolemia and anemia is apparent. Failure to utilize blood transfusions for these purposes may result in death, as unfortunately occurred in Case 6. The role of blood transfusions in correcting alterations in the hemostatic mechanism associated with abruptio placentae is less clear.

The fibrinogen content of the plasma of blood collected from apparently normal donors into ACD solution was measured before and after storage. As shown in Table II, the fibrinogen concentration initially was rather low but showed no further decrease after storage. The average plasma fibrinogen concentrations of blood bank blood were as follows: immediately after collection, 194 mg. per 100 ml.; stored one through 7 days, 194 mg. per 100 ml.; stored 8 through 14 days, 198 mg. per 100 ml.; and stored 15 through 21 days, 192 mg. per 100 ml.

TABLE II. THE CONCENTRATION OF FIBRINOGEN IN PLASMA OF BLOOD FROM NORMAL DONORS AFTER COLLECTION IN ACD SOLUTION AND EITHER ASSAYED IMMEDIATELY OR STORED UP TO 21 DAYS

	IMMEDIATE	1-7 DAYS	8-14 DAYS	15-21 DAYS
Average	194	194	198	192
Range	164-234	170-226	169-243	152-238

Comment.—A specific search for hypoprothrombinemia and accelerator globulin deficiency, two abnormalities which have been noted previously in abruptio placentae,[6, 7] was not made, but observations in these cases indicate that the hemostatic defect of clinical significance in abruptio placentae is hypofibrinogenemia, for hemostasis was promptly achieved after correction of the fibrinogen deficit, even though at least one other demonstrated defect in the hemostatic mechanism, thrombocytopenia, persisted.

The use of blood collected in the standard fashion in ACD solution, whether the blood be fresh or simply obtained from available stock, is of little value when used for the specific purpose of attempting to raise the plasma fibrinogen level. The minimal plasma level to guarantee against hemorrhage from hypofibrinogenemia is probably about 125 to 150 mg. per 100 ml. Since the concentration in the plasma of bank blood is, on the average, only 195 mg. per 100

ml., such blood can donate only 45 to 70 mg. of fibrinogen for each 100 ml. of plasma administered. Therefore each unit of blood transfused, whether it be fresh or stored, contributes less than 0.3 Gm. of fibrinogen toward overcoming the fibrinogen deficiency, whereas the amount actually needed usually is at least 3 Gm. It is apparent that therapy with blood equivalent to nearly a complete exchange transfusion would be necessary in cases of severe hypofibrinogenemia to raise the plasma level to 125 to 150 mg. per 100 ml.

5. When should specific fibrinogen replacement therapy be instituted?

The administration of human plasma and several of its protein fractions carries with it the inherent risk of homologous serum jaundice. In one recent report 7 of 16 patients who received fibrinogen developed this disease, a disease which can either rapidly kill or produce serious chronic impairment of liver function.[9]

Four hundred nine members of the Central Association of Obstetricians and Gynecologists reported their experiences in treating 727 patients with fibrinogen. It must be assumed that practically all of these patients received blood, not infrequently in relatively large volumes: Thirty-seven of these patients were known to have developed homologous serum jaundice, an incidence of 5 per cent. One of the 37 died of homologous serum jaundice.

Comment.—The answer to the question when fibrinogen should be given is not simple. It is obvious that the possibilities for the use of fibrinogen range from giving it to every patient who is bleeding, and in so doing perhaps achieving both diagnosis and therapy, to the other extreme of never administering it and, instead, treating the patient with hypofibrinogenemia and abruptio placentae with only those modalities advocated prior to this decade.

The presence of hypofibrinogenemia can be ascertained rapidly by the simple clot observation test described above. Therefore, to give fibrinogen to bleeding patients without first establishing the presence of hypofibrinogenemia is to be condemned. To be economically feasible, relatively large pools of human plasma must be used in its preparation. As a result there is a very real risk of contamination with the virus which causes homologous serum jaundice. It is not surprising that the incidence of homologous serum jaundice was at least 5 per cent in the 727 patients who received fibrinogen. Since there frequently is a long latent period between administration and clinical evidence of the disease, there undoubtedly are several more cases not known to the obstetricians who cooperated in this survey.

On the basis of observations made in several of the cases in this study it appears equally absurd to adopt the other extreme and never administer fibrinogen. When the plasma fibrinogen level approaches 100 mg. per 100 ml. or less, the deficit should be corrected prior to any operative procedure which would result in deliberate incision of blood vessels. Laparotomy in Cases 7 and 8 resulted in further hemorrhage of life-endangering proportions which was brought under control, not by hysterectomy, but by the administration of fibrinogen. In 2 similar situations, Cases 9 and 10, laparotomy was carried out immediately after adequate fibrinogen therapy with no abnormal bleeding.

In the instances in this series where delivery was carried out with neither trauma nor deliberate incision of blood vessels in the genital tract, postpartum hemorrhage was not encountered as long as the uterus remained firmly contracted, even though severe hypofibrinogenemia persisted. Therefore, fibrinogen therapy is not mandatory in all cases of abruptio placentae with hypofibrinogenemia. Even though the administration of fibrinogen may not always be necessary to prevent exsanguination in cases of abruptio placentae with severe hypofibrinogenemia, the risks resulting from withholding fibrinogen

therapy frequently may be greater than those associated with its administration. Certainly, if any operative interference is contemplated, if an anesthetic agent which might contribute to decreased myometrial tone is to be administered, if extensive genital tract lacerations are encountered, or if the uterus will not remain firmly contracted after delivery, fibrinogen therapy is not only indicated but may be lifesaving.

Summary and Conclusions

Severe hypofibrinogenemia, when it occurs, frequently may develop within 6 hours following the onset of symptoms of abruptio placentae.

Blood loss from the site of implantation of the placenta during the early puerperium is not excessive in abruptio placentae with uncorrected hypofibrinogenemia if there is sufficient myometrial tone. When blood vessels are severed elsewhere in the body, a mechanism capable of providing comparable vasoconstriction does not exist.

After the uterus is emptied the plasma fibrinogen concentration rises in roughly linear fashion. Eight to 12 hours usually elapse before the plasma fibrinogen reaches a level adequate for satisfactory clot formation. Thrombocytopenia is corrected at a much slower rate than is hypofibrinogenemia.

The alteration in the hemostatic mechanism of clinical importance in abruptio placentae is hypofibrinogenemia. The administration of normal blood collected in ACD solution, either fresh or stored, is of little value when used specifically to correct fibrinogen deficiency.

The administration of fibrinogen to bleeding patients without the presence of hypofibrinogenemia being established is condemned. The injection of fibrinogen (usually with whole blood) is followed by homologous serum jaundice in at least one out of every 20 patients so treated.

While the administration of fibrinogen is not absolutely necessary in all cases of abruptio placentae with severe hypofibrinogenemia, the hypofibrinogenemia should be corrected at least in instances where an operative procedure is to be performed, an anesthetic agent which might contribute to decreased myometrial tone is to be administered, genital tract lacerations have been encountered, or the uterus does not remain firmly contracted after delivery.

References

1. Page, E. W.: Discussion of Kellogg, F. S.: Obst. & Gynec. Surv. 3: 746, 1948.
2. Ratnoff, O. D., Colopy, J. E., and Pritchard, J. A.: J. Lab. & Clin. Med. 44: 408, 1954.
3. Weiner, A. E., Reid, D. E., and Roby, C. C.: Am. J. Obst. & Gynec. 66: 475, 1953.
4. Jackson, D. P., Hartmann, R. G., and Busby, T.: Obst. & Gynec. 5: 223, 1955.
5. Ratnoff, O. D., Pritchard, J. A., and Colopy, J. E.: New England J. Med. 253: 63, 97, 1955.
6. Moloney, W. C., Egan, W. J., and Gorman, A. J.: New England J. Med. 240: 596, 1949.
7. Johnson, R. F., Seegers, W. H., and Braden, R. G.: Am. J. Clin. Path. 22: 322, 1952.
8. Barnes, A. C.: Am. J. M. Sc. 213: 463, 1947.
9. Skinner, J. S.: Missouri M. A. J. 54: 740, 1957.

Discussion

DR. WILLIS E. BROWN, Little Rock, Ark.—There is one aspect of this presentation that I should like to emphasize and explore further. The author has demonstrated that there is no direct relationship between uterine bleeding and the blood levels of fibrinogen.

He points out that, if the patient does not go into shock or is not so anesthetized that the uterus relaxes, uterine contraction adequately controls bleeding even in the face of hypofibrinogenemia. Thus the contraction of the postpartum uterus is the most important mechanism in the control of genital bleeding when hypofibrinogenemia is present.

The author has wisely avoided the old classification of either radical or conservative management. It has unfortunately been utilized to mean abdominal or vaginal delivery. We are convinced that the route of delivery is of less importance than the aggressiveness of obstetric care. It may be suggested that not only does uterine contraction control postpartum bleeding, but it also prevents the development of hypofibrinogenemia.

At the University of Arkansas, it had been the policy to perform a cesarean section on all patients with severe abruptio placentae and to observe the others. In 1949, the policy was changed to the prompt induction of strong uterine contraction in anticipation of vaginal delivery. The abdominal route was reserved for the other usual obstetric indications and for the occasional refractory case.

From 1940 through 1956, there were 243 cases of abruptio placentae—80 from 1940 to 1949, and 163 from 1950 through 1956. In this series, the aggressive induction of strong uterine contraction provided better clinical results in terms of live mothers and babies.

Perhaps more important from the standpoint of this discussion is the incidence of clinical hypofibrinogenemia. In the 80 patients from 1940 to 1949, there were 5 whose records indicated probable hypofibrinogenemia and 2 deaths from generalized bleeding. From 1950 through 1956, there was only one case in 163 with this clinical syndrome.

Thus we believe that the aggressive approach to abruptio placentae should replace the "masterful inactivity" or "watchful expectancy" concept, and that if the control of dissemination of thromboplastin is attacked promptly it matters little whether this is done abdominally or vaginally.

The term "radical" should be reserved for those who watch expectantly, and the term "conservative" should be applied to obstetricians who adopt systems that contract the uterus promptly and aggressively, either by emptying it abdominally or stimulating its contraction chemically.

VULVECTOMY FOR BENIGN VULVAR DISEASE: INDICATIONS, TECHNIQUE, AND RESULTS*†

CONRAD G. COLLINS, M.D., RICHARD G. BURMAN, M.D.** DONALD McMAHON, M.D., AND JAMES K. AVENT, M.D., NEW ORLEANS, LA.

(From the Department of Obstetrics and Gynecology, Tulane University School of Medicine and the Tulane Unit, Division of Obstetrics and Gynecology, Charity Hospital of Louisiana, New Orleans)

DURING the period Jan. 1, 1946, to Jan. 1, 1957, there were 87 vulvectomies performed at Charity Hospital by the staff, residents, and fellows of the Department of Obstetrics and Gynecology, Tulane University (Table I). Though a number of different individuals cared for and operated upon these patients, a rigid protocol as to preoperative survey, indications for operation, postoperative care, operative technique, suture material, and scope of operation was strictly pursued by common consent. In this manner we are at present able to evaluate the results attained by a group of individuals following a set of what we believe to be basic policies in the management of vulvar lesions.

TABLE I. VULVECTOMIES FROM JAN. 1, 1946, TO JAN. 1, 1957

For malignant lesions		46
Intraepithelial	6	
Invasive	40	
For benign lesions		41
Total		87

Vulvectomy was utilized as definitive therapy or as part of the surgical procedure in 46 cases of malignant and premalignant disease involving the vulva. If multiple sections of the extirpated vulva fail to reveal invasion we are fairly certain that the malignant process is intraepithelial and consider vulvectomy sufficient therapy. Our results justify this contention.[1] If on biopsy or on multiple section of the extirpated vulva an invasive malignant process is determined, then, in addition to vulvectomy, bilateral regional node dissection is performed. This encompasses removal of the superficial and deep inguinal, femoral, Cloquet's, external iliac, hypogastric, common iliac, obturator, and lower aortic and vena cava nodes. Should the malignant process involve organs or structures other than the vulva, then additional procedures

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**Gulfport, Miss.

up to and including total exenteration are utilized as indicated. Our results and experiences in the management of invasive malignancy have been recorded elsewhere.[2-5]

This report concerns the 41 cases in which vulvectomy was performed for benign lesions. It is to be emphasized that the scope of the operation of vulvectomy on our service is the same for the therapy of benign as for malignant lesions, with two exceptions. These exceptions are: in dealing with invasive malignancy the contents of both ischiorectal fossae are removed; and, when malignancy involves contiguous structures, these structures are also extirpated.

Indications

Our indications for vulvectomy in benign disease fall roughly into two main categories. The first is the failure of vulvar tissues to return to normal following medical treatment for chancroid, granuloma inguinale, lymphogranuloma venereum, or syphilis. It has been our experience,[1] as well as that of others,[6] that a reasonable number of cases of malignancy of the vulva may be the result of, associated with, or develop in, vulvar tissues that remain hyperplastic and/or hypertrophic following apparently successful control or cure of the initial infection. The second group includes the cases of vulvar disease in which the symptoms of itching, pain, bleeding, fissuring, or ulceration, alone or in combination, persist following an extensive diagnostic survey and specific or general medical therapy. Conversely, if on biopsy of a vulva without symptoms, a report of leukoplakia, kraurosis, lichen sclerosus et atrophicus, or other benign disease is obtained, no treatment is initiated. The patient is observed at frequent intervals and only should one or more of the afore-mentioned symptoms appear is vulvectomy performed. When such symptoms do develop in vulvas exhibiting leukoplakia, kraurosis, or lichen sclerosus et atrophicus, the whole vulva is submitted to the pathologist for study of multiple sections and reliance is not placed upon single or multiple biopsy specimens. Our other indication for vulvectomy, of course, is the presence of a tumor.

As previously stated, many times the indication for vulvectomy is predicated upon the persistence of the symptoms of burning, itching, or pain about the vulva. Therefore it is necessary to perform a detailed study of each case in order that a specific etiological agent may be discovered and the application of a proper medical regimen utilized to produce desired results. The means and method of this type of survey on our service have been recorded elsewhere.[7]

TABLE II. AGE OF PATIENTS TREATED FOR BENIGN DISEASE OF THE VULVA

AGE	NO. OF PATIENTS
10-19	1
20-29	4
30-39	6
40-49	8
50-59	6
60-69	9
70-80	7
Total	41

We do not consider youth or old age a contraindication to vulvectomy. The youngest patient in this series was 19 years old; a vulvectomy was performed for a myeloblastoma of the vulva one and one-half years ago. At present she is 26 weeks pregnant and a normal delivery is expected. Seven patients were over 70 years of age when operated upon (Table II). There was no death, nor was

there any difference noted in wound healing in any age group. Sixteen of the patients were Negro and 25 were white. Here again no difference was noted between the two groups with regard to postoperative course, wound healing, or end result.

The presenting symptoms in all but 4 patients were itching about the vulva, pain, bleeding, ulcers or "sores," discharge, or tumor masses. Pruritus was by far the most prominent, being encountered in 23 of the 41 patients. Most frequently more than one of the afore-mentioned symptoms was present in each patient. In only 5 patients had the symptoms been present less than one year when first seen by us. In 75 per cent of the cases symptoms had been present for more than 2 years. Most of the patients had had previous therapy in the form of ointment, lotions, or salves to the vulva. In 8 cases persistent hypertrophic and/or hyperplastic tissue, following treatment for venereal disease, or tumor masses were encountered.

In no case was there a history of x-ray therapy to the vulva. At this point it is pertinent to mention that irradiation of any sort to the vulva is not used by us in the treatment of either benign or malignant lesions involving the vulva.

There was involvement of the whole vulva in 27 individuals. In 5 the area affected was less than 2 cm. in diameter, while in the remainder of the cases the lesions varied from 2 to 11 cm. in size. Other portions of the vulvar area involved included the clitoris in 6 and the perianal area in 9 patients. It is to be emphasized that extensive vulvectomy was performed in all patients irrespective of the size or location of the lesion. In no case was vulvectomy not performed when deemed necessary because of the patient's general medical condition.

Technique

The technique to be described has been used on our service since Jan. 1, 1946. It is simple, rapid, extensive, with minimal blood loss and excellent wound healing. In the vast majority of instances less than 10 hemostats had to be applied to control bleeding. Buried sutures are of cotton No. 40. The cosmetic and functional results are superior to those attained by any other method we have previously used. Anesthesia is no problem. In Table III the types of anesthesia employed are recorded.

TABLE III. ANESTHESIA EMPLOYED IN SERIES

TYPE	NO. OF PATIENTS
General—inhalation	22
Spinal	18
Local	1
Total	41

The area to be removed is outlined on the skin and vaginal mucous membranes. The primary consideration of the operation is to remove diseased tissue with a wide margin of normal tissue and thus lessen any chance of recurrence. The lateral margins of the incision should always be distal to the labia majora, minora, clitoris, and fourchette (Fig. 1). The medial margins are always medial to the labia minora and include as much of the vaginal mucous membrane as necessary. In some cases one need not go any higher than the hymenal ring. When outlining the area to be excised, one should not worry about removing too much tissue, but rather be certain that enough is being removed. No thought should be entertained as to how tissues are to be approximated until all tissue necessary to accomplish cure is removed. In nearly every

case, no matter how wide the excised area, reapproximation of the vaginal mucous membrane to skin can be effected. This was possible in all our operations for benign disease. In some cases where malignant lesions made it necessary to carry the dissection out into the thigh and primary approximation could not be effected completely, the wounds healed by second intention within a few weeks. As a matter of fact it would seem to be very difficult to prevent rapid healing of any defect.

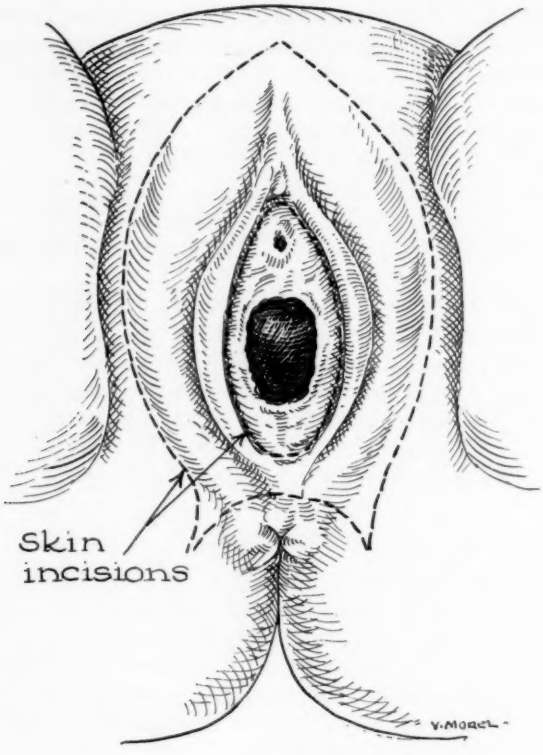

Fig. 1.

After we have outlined the lateral and medial margin of the area to be excised, an index finger of the surgeon and an index finger of an assistant are placed parallel to each other over the pubic bone and an incision approximately 1 inch long and down to the periosteum of the pubis is made (Fig. 2). The index finger of the surgeon and an index finger of an assistant are then placed in the incision and by means of finger dissection along the deep fascia the vulvar skin, fat, and connective tissue are separated from the underlying fascia. This is one of the most important steps in the operation (Fig. 3). The dissection is carried out medially, laterally, and caudad in the same manner. The freed skin, fat, and connective tissue are then pulled outward by the underlying fingers and the incision continued along the outline previously made. The dissection is carried out in this manner until the area between the tuberosity of the ischium and the anus is reached. The index finger of the surgeon then explores this area and the external pudendal artery, nerve, and vein are easily identified as they leave Alcock's canal. They are clamped, cut, and ligated at this point. The procedure is then repeated on the other side of the vulva (Fig. 4).

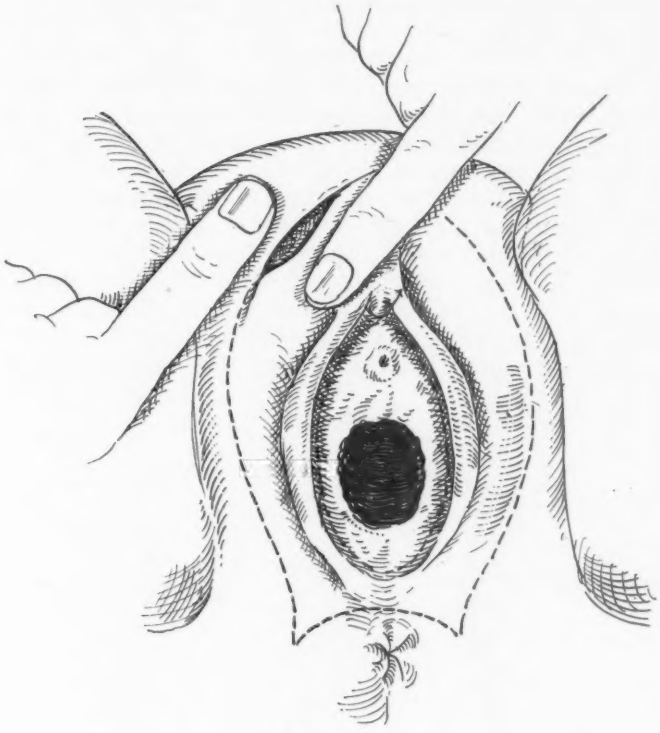

Fig. 2.

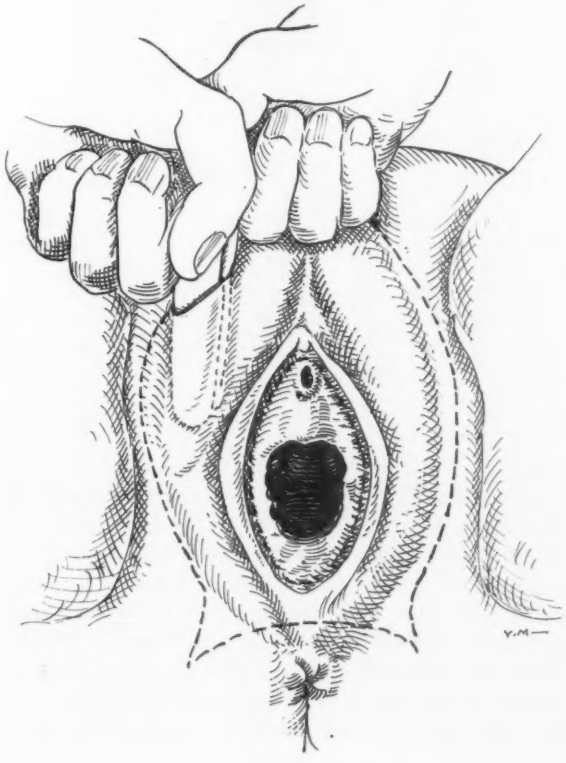

Fig. 3.

The index finger of the surgeon then frees skin, fatty and connective tissue from the external oblique and rectus fascia, and the incision is continued through these structures to join in the midline. By means of sharp and blunt dissection the tissues are separated from the periosteum of the anterior surface of the symphysis until the base of the clitoris is reached. The clitoral artery and veins are clamped and ligated. The dissection is carried to the urethral wall. The labia majora, minora, fatty and connective tissue are then swept medially until the lateral surface of the levator muscles is encountered. The dissection then continues medially along the fascia of the levator muscles. Thus the vulva and all fat and connective tissue down to the fascial layers, except posteriorly, have now been freed. The skin, fat, and connective tissue are then separated from the anus and rectum. This leaves the vulva completely free except for the vaginal mucous membrane. The vaginal mucous membrane is then cut along the outline previously established and the vulva extirpated.

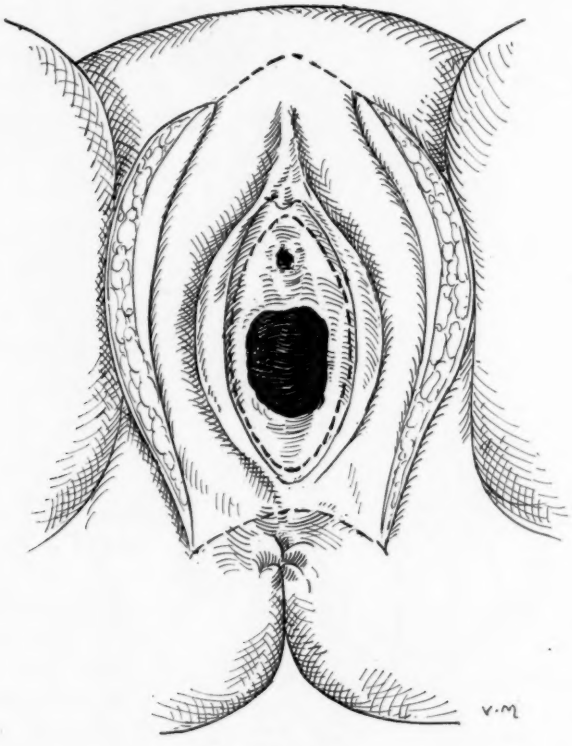

Fig. 4.

The margins of the vaginal mucous membrane are then grasped with Allis forceps. The attachment of the levator ani muscles to the vaginal mucous membrane, laterally as well as posteriorly, is cut, and the vaginal mucous membrane completely freed from these structures (Fig. 5). The edges of the freed levator muscles are then sutured just beneath the medial margin of the skin. This procedure pulls the inferior margin of the levators laterally. This step in the operation serves two important functions. In the first place, much of the deep raw area is covered and, in the second instance, tension will be less on the suture line when skin and mucous membrane are coapted. Three sutures on each side are utilized for this purpose (Fig. 6). Up to this point

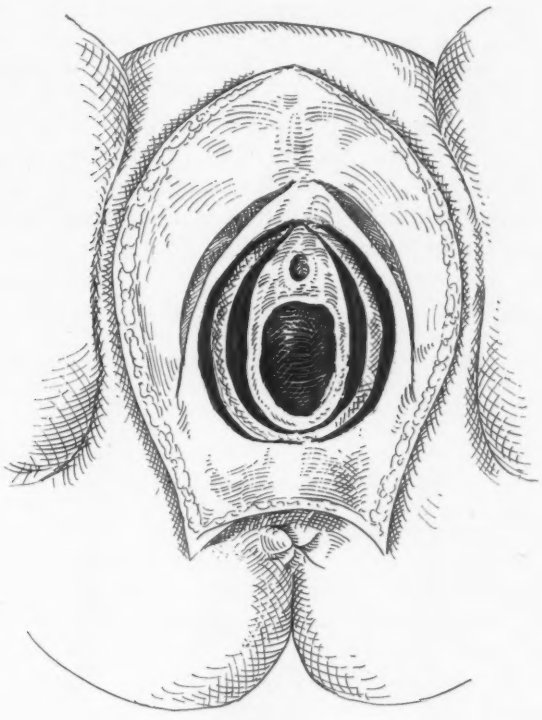

Fig. 5.

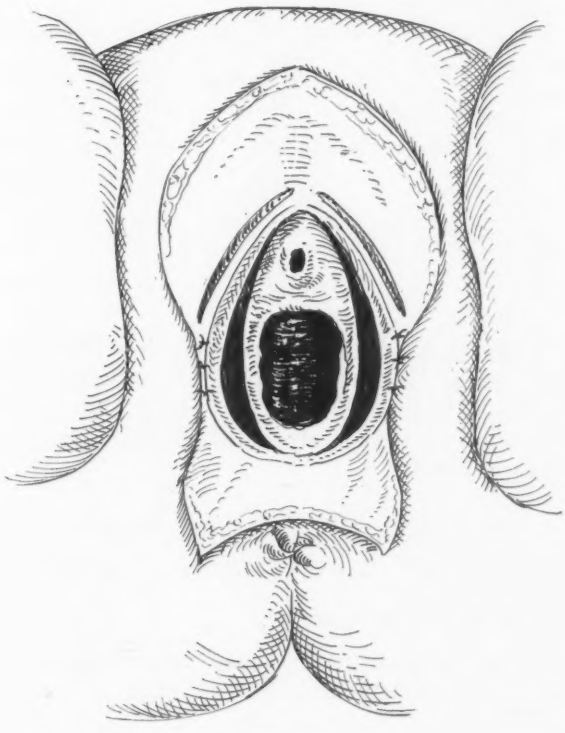

Fig. 6.

all sutures and ligatures are of interrupted cotton No. 40. Interrupted sutures of the same material are placed in the submucous layer and subcutaneously 1 cm. apart, and the mucous membrane and skin are brought together throughout the entirety of the incision. An external layer of interrupted chromic No. 3-0 catgut produces final coaptation of skin and mucous membrane. Thus all buried sutures are of cotton No. 40. The external sutures are of fine catgut, though cotton may be used. We prefer catgut for the external layers as the patient is spared the removal of sutures in this area, which at times can be inconvenient, difficult, and time consuming (Fig. 7).

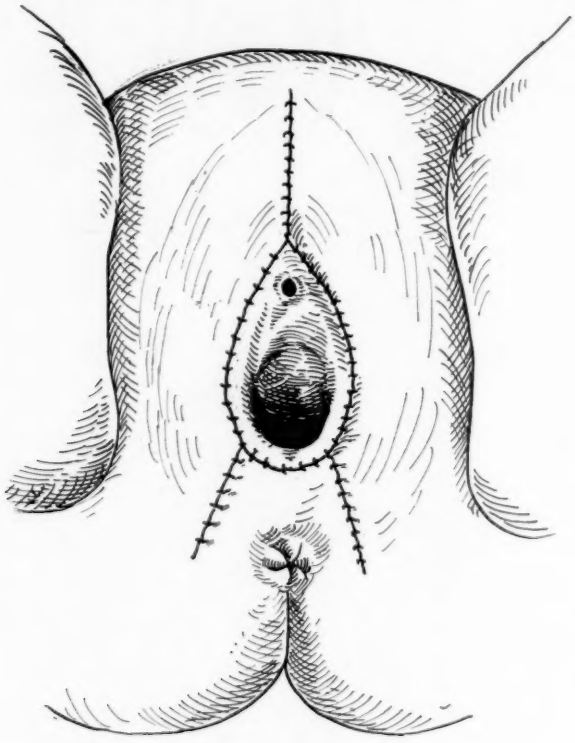

Fig. 7.

Any additional gynecologic procedure needed can be performed at the same time. In this series this was done in 10 instances (Table IV). When vaginal hysterectomy is indicated at the time of vulvectomy, extirpation of the vulva is followed by vaginal hysterectomy, and then closure of the vulvar defect expedites the operation.

TABLE IV. GYNECOLOGIC PROCEDURES IN ADDITION TO VULVECTOMY

TYPE	NO. OF PATIENTS
Vaginal hysterectomy with plastic	2
Vaginal plastic	2
Total abdominal hysterectomy with salpingo-oophorectomy	1
Abdominal hernia repair	1
Rectovaginal fistula	1
Trachelectomy	2
Curettage	1
Total	10

Results

We have found that there is no shock associated with the procedure done by this technique. Postoperatively the patient is very comfortable, and there usually is no need for opiates or sedatives after the first 24 hours. A retention catheter is placed in the bladder at completion of the operation and removed within 48 hours. The patient is ambulated immediately upon recovery from anesthesia and following removal of the catheter has full bathroom and shower privileges. She cares for her own perineum, no special nursing care or medicaments being needed at the operative site.

In 30 cases the wound healed by primary intention. In 11, there was slight breakdown of the wound in one area or the other, which did not extend hospitalization or convalescence. All healed by secondary intention with more than satisfactory end result. Follow-up examinations have been carried on in the "Vulvar Clinic," maintained by the Department of Gynecology, Tulane University, in which a member of the Department of Dermatology is present at all times. Follow-up has been adequate in all cases except one. This patient was last seen 3 months after operation, at which time the wound was well healed and she did not have any complaints. The remaining 40 patients have been seen over periods of one to 9 years. In 6 cases further minor procedures were performed. In 4 of these, excision of part of the scar was performed because of a painful area. In 2, the skin near the urethral meatus formed a fold so that when the patient urinated the stream was deflected; therefore excision of this "dashboard" was done. In no case has there been a recurrence of the symptoms or pathological conditions for which the operation was performed. Twenty of the patients were still young enough to be interested in sexual intercourse. Of these, intercourse was normal and orgasm attained in 17. Three others reported that intercourse was engaged in but there was no orgasm. Two of the 3, however, did not have orgasm on intercourse prior to operation. Three of the patients have become pregnant since operation. One has become pregnant twice since operation and each time was delivered normally per vaginam without complication. Each child weighed over 7 pounds. Another was delivered of a term 8 pound baby normally per vaginam without any complications. A third patient is now 26 weeks pregnant and a normal delivery is contemplated.

TABLE V. MICROSCOPIC DIAGNOSIS

	NO. OF PATIENTS
Leukoplakia	4
Kraurosis	6
Lichen sclerosus et atrophicus	1
Neurofibroma	2
Chronic vulvitis	17
Elephantiasis	1
Fibroma	1
Hyperkeratinization	1
Seborrheic keratosis	1
Leiomyoma	1
Condylomata acuminata	2
Radiation reaction	1*
Granuloma inguinale	3
Lymphangioma	1
Myeloblastoma	1

*X-ray and radium for carcinoma of cervix.

Microscopic Diagnoses

In this series of 41 cases there were 15 different disease entities diagnosed on microscopic examination of multiple sections made from the excised vulva (Table V). It is to be noted that leukoplakia was reported only 4 times,

kraurosis 6 times, and lichen sclerosus et atrophicus only once. This emphasizes our previous statement that we do not recommend or perform vulvectomy simply because a biopsy report of these entities is received. Only when symptoms such as fissuring, itching, burning, bleeding, or pain, alone or in combination, persist despite extensive diagnostic survey and application of medical therapy, is vulvectomy performed. In 17 cases a diagnosis of chronic vulvitis was reported; these patients are all relieved of their symptoms. The one common denominator, with the exception of the cases in which vulvectomy was performed because of tumor masses or residue of venereal disease, is the persistence of symptoms.

Comment

Partial vulvectomy, hemivulvectomy, or "simple vulvectomy" is not used on our service for the treatment of benign or malignant lesions. Extensive (radical) vulvectomy, comprising wide lateral and deep dissection to the fascial structures, is employed for the treatment of benign lesions and intraepithelial carcinoma. Extensive vulvectomy with regional node dissection and excision of contiguous structures, if necessary, is utilized for invasive malignancy. Timidity has no place in the attempt to cure benign or malignant lesions of the vulva. Of course, local excision of sebaceous cysts, hydradenomas, small fibromas, and nonmalignant moles is employed, but this really amounts to excision biopsy performed in the same manner as if these lesions were elsewhere on the body. When the disease process is one of the vulvar integument, however, or if the tumor masses are large, then vulvectomy is performed. The cosmetic as well as functional results of total extensive vulvectomy, in our hands, have been far more successful and satisfactory than the results attained in the period prior to 1946 when we utilized less extensive procedures. Of course, many, for no rational reason, consider vulvectomy a mutilating operation.

Extensive vulvectomy, in addition to producing cure, allows the pathologist to make multiple sections to prove whether the disease is benign, intraepithelial carcinoma, or invasive malignancy. In the 6 cases of intraepithelial carcinoma encountered on our service, preoperative biopsy report of intraepithelial carcinoma was confirmed on study of multiple sections of the excised vulva. In one case, however, the preoperative biopsy report of benign disease was proved incorrect, as, on multiple section of the excised vulva, noninvasive carcinoma was encountered. Furthermore, when a diffuse vulvar lesion is encountered, the problem arises as to which area should be biopsied. This is especially true in lesions in which, despite an extensive diagnostic survey and the application of recommended specific and/or general medication, no improvement is noted in symptoms or appearance. This type of case is one of our primary indications for extensive vulvectomy. The results attained leave us no choice but to pursue this course.

In addition to the anatomic, functional, and cosmetic results attained by the use of the technique described, we wish to re-emphasize that this technique also has the following advantages: minimal blood loss, very little postoperative pain, minimal nursing care, primary wound healing in most cases; there is no shock, and the procedure can be performed under any type of anesthesia.

During the period Jan. 1, 1946, to Jan. 1, 1957, there have been more vulvectomies performed on our service for malignant than for benign disease. Though the vulva is the most accessible area of the female genital tract, there has apparently been less study of disease of this area or the studies made have been less productive than research performed on other organs of the female genital tract. Much remains to be learned concerning disease of this area.

Certainly cancer involving the vulva should be detected early but there is still a certain amount of delay on the part of both patient and physician. Some seem to be hesitant to subject this area to biopsy unless ulceration is present, or they are reluctant to remove the whole of the vulva for persistent symptomatic benign or malignant disease, possibly because of the thought that vulvectomy is a mutilating operation. We have recently established a "Vulvar Clinic" at Tulane in conjunction with the department of dermatology. A dermatologist well acquainted with the histopathology of the skin, as well as the pathologists, studies tissue removed by biopsy or vulvectomy. We hope in this way to learn more about the diseases involving this area. Whether or not chronic irritation is an etiological agent in carcinoma of the vulva is equivocal. We do know that the symptoms of pruritus and pain are extremely annoying to the patient, and, until more study can show cause and effect in many conditions involving the vulva, extensive vulvectomy is indicated in resistant cases.

References

1. Collins, C. G., Kushner, J., Lewis, G. N., and Lapointe, R.: Obst. & Gynec. 6: 339, 1955.
2. Collins, C. G., Collins, J. H., Nelson, E. W., Smith, R. C., and MacCallum, E. C.: Am. J. Obst. & Gynec. 62: 1198, 1951.
3. Collins, C. G., Collins, J. H., Nelson, E. W., Lewis, G. N., and Cassidy, R. E.: Obst. & Gynec. 8: 18, 1956.
4. Collins, J. H., Burman, R. G., and Mathews, N. M.: Am. J. Surg. 92: 37, 1956.
5. Cassidy, R. E., Braden, F. R., and Cerha, H. T.: Am. J. Obst. & Gynec. 74: 361, 1957.
6. Saltzstein, S. L., Woodruff, J. D., and Novak, E. R.: Obst. & Gynec. 7: 80, 1956.
7. Collins, J. H., and Ellington, C. J., Jr.: New Orleans M. & S. J. 104: 220, 1951.

Discussion

DR. N. PAUL ISBELL, Denver, Colo.—The type of vulvectomy so clearly demonstrated by the authors takes advantage of a natural line of cleavage at the level of the deep fascia and the covering of the levator muscles. This facilitates the dissection and at the same time provides natural landmarks. In this manner, fewer bleeding vessels are encountered and the subcutaneous fat and connective tissue with the important lymphatic channels are removed en masse. If invasive malignant disease is found in the specimen, it is then much easier to complete the removal of the remaining lymphatic systems since all of the lymphatics of the medial area have been removed with the specimen.

The initial wide incision not only insures safe removal of the lesion but also lessens the minor though annoying tendency of remaining hair continually to collect secretions and to irritate the vaginal mucosa and urethral meatus.

Many women suffer in silence and develop numerous nervous and emotional symptoms because they have pruritus and cannot scratch for fear of detection. On the other hand, some women will develop emotional disturbances after a vulvectomy in much the same manner as occurs at times after a mastectomy. It is important that the candidates for vulvectomy be mentally conditioned for it prior to the operation. It is essential that intercourse be discussed and the patient know that she will be able to continue a normal marital relationship.

It is true that malignant disease may develop in hyperplastic or hypertrophic tissues remaining after vulvar infections but this is not to be confused with the atrophic vulvar membranes that remain after the chronic vulvitis is relieved.

It is interesting to note that this series does not contain any cases requiring vulvectomy because of previous ill-advised x-ray therapy.

It is well to remember that although a safe and relatively simple surgical procedure with unusually fine results has been presented, we must be careful not to extend its use to conditions not indicated by the authors, which might be safely treated by more conservative methods.

EVALUATION OF HYPOTENSIVE DRUG THERAPY IN CHRONIC HYPERTENSIVE DISEASE IN PREGNANCY*†

WILLIAM J. DIECKMANN, M.D.,‡ AND
JOHN P. HARROD, JR., M.D., CHICAGO, ILL.

(From the Chicago Lying-in Hospital, University of Chicago)

DURING the past five and a half years we have been evaluating the beneficial or detrimental effects of long-term hypotensive drug therapy on the mother and/or the fetus in cases of chronic hypertensive disease complicated by pregnancy. During this period the diagnosis of toxemia of some degree and type has been made in 1,100 patients at the Chicago Lying-in Hospital. As can be seen from Table I, 118 of these patients had chronic hypertension with a systolic blood pressure in excess of 180. Our control period, insufficient time, etc., eliminated all but 20 who were suitable candidates for hypotensive drug therapy.

TABLE I. TOXEMIA OF PREGNANCY IN 118 PATIENTS WITH BLOOD PRESSURE IN EXCESS OF 180 SYSTOLIC*

Responded to bed rest	30
Therapeutic abortion	25
Treated with hypotensive drugs	20
Insufficient time for therapy†	43
Total	118

*Two or more readings 12 hours apart.
†Went into labor, labor induced, etc.

Selection of Cases

No patients with pre-eclampsia-eclampsia are included. We have always felt that the blood pressure in this group is compensatory and its height is of little or no prognostic value. Forty-five per cent of our cases of toxemia are pre-eclampsia-eclampsia. The blood pressure in these cases rarely reaches a dangerous level but in the patients whose systolic pressure remained at a level of 200 plus we have lowered the pressure with some type of intravenous hypotensive therapy. These cases are not included in this study because the time of therapy was always too short to allow proper evaluation as to beneficial or detrimental effects on the fetus. Kellar[1] reported on the use of hypotensive drugs in the treatment of imminent eclampsia and found no evidence that any of the drugs caused a fundamental improvement in the pre-eclamptic process. Because, however, of the reported cases of fetal neonatal ileus, he

*Abstracted in the Proceedings of the Central Society for Clinical Research for 1957.
†Presented at the Twenty-fifth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Omaha, Neb., Oct. 24, 25, and 26, 1957.
‡Died, Aug. 15, 1957.

did not use any of the ganglion-blocking drugs. In the discussion of his paper Townsend stated that he gave hexamethonium bromide to 55 pre-eclamptic patients and only one developed eclampsia, but there were 6 fetal deaths and one maternal death, while in his control study of 92 cases, there were 8 who developed eclampsia, no maternal deaths, and 8 fetal deaths.

Recently we have been given a case report from another hospital (Fig. 1) of an eclamptic patient who prior to her first convulsion was given intravenous Apresoline. She began having convulsions even with the lowered pressure, continued convulsing, and remained in coma until her death which was preceded by a nearly normal blood pressure.

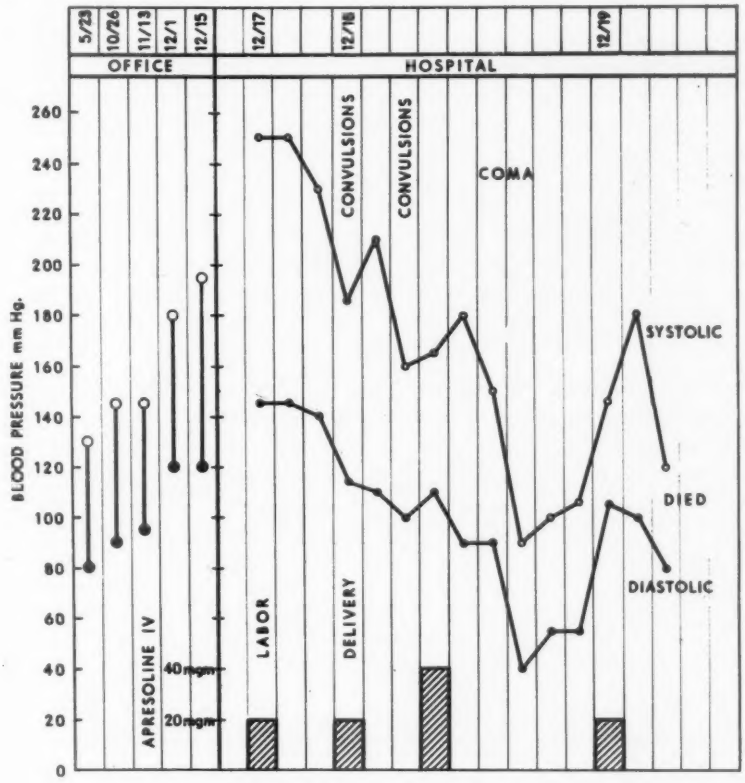

Fig. 1.—Patient with eclampsia treated with intravenous Apresoline.

The only significant accomplishment that we have been able to obtain with hypotensive therapy is to lower the blood pressure. In no case have we been able to decrease proteinuria to a significant degree. With this in mind, we have limited the cases to those with a blood pressure of 180/110 or higher. At this pressure Dieckmann[2] believed that in the young patient cerebral hemorrhage is likely to occur.

Many reports in the literature on hypotensive therapy in hypertensive toxemia have either ignored or overlooked the known beneficial effects of hospitalization without therapy on essential hypertension. They have started therapy as soon as the patient is hospitalized. Their results have been good. All of our patients have been admitted to an air-conditioned room and placed on bed rest and a low-sodium and -potassium diet for 48 hours or longer, prior to therapy. Thirty of our patients who would have made excellent candidates

for therapy were thus eliminated. These 30 patients (as can be seen in Table II and Fig. 2) had blood pressures at normotensive levels or at levels so nearly normotensive that no therapy was indicated. Only one of these (3.3 per cent) did not leave the hospital with a live infant. One other patient was aborted because of severe renal damage.

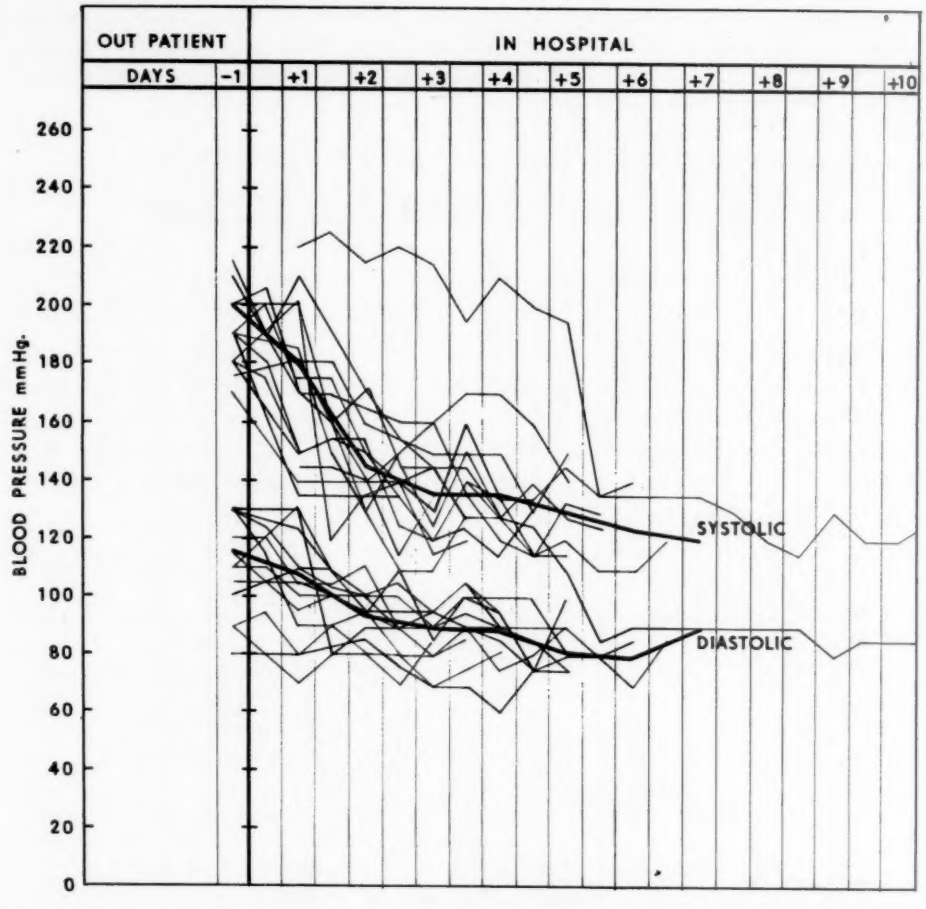

Fig. 2.—Effect of hospitalization alone on blood pressure. Light lines show individual cases whereas heavy lines show average systolic and diastolic pressures.

TABLE II. EFFECT OF BED REST ALONE ON BLOOD PRESSURE

BLOOD PRESSURE	NO. OF OUT PATIENTS	HOSPITAL DAY					
		1	2	3	4	5	6
Systolic.—							
Average	200	178	144	136	136	130	123
Maximum	250	225	220	195	200	150	135
Minimum	170	135	110	110	115	110	110
Diastolic.—							
Average	116	108	94	90	88	82	80
Maximum	145	145	140	130	125	100	90
Minimum	85	80	70	70	75	75	70

In recognition of the decreased fetal survival rate and the increased maternal risk that accompany pregnancy associated with hypertension in its

early stages, all candidates thus far eligible were offered therapeutic abortion. During the period of this study we had 25 women who had therapeutic abortions performed for renovascular disease; thus our eligible candidates were further reduced.

Still another 43 patients with elevated blood pressures were eliminated because of lack of time to evaluate, for they were either in labor or near enough to having a viable infant to warrant induction.

Evaluation of Drugs

By using the above criteria of selectivity we were left with only 20 patients who, we felt, were suitable candidates for evaluation of any beneficial or detrimental effects. Table III shows the types of drugs that were used. With so few patients and so many drugs being evaluated, it was very difficult to access the dosage adjustments and other problems incurred by the use of such powerful drugs. Hence many of our gynecologic or postpartum hypertensive patients with essential hypertension above 180/110 who have been willing to let us follow them have likewise received hypotensive therapy for periods up to four years in duration. These on the whole have been much easier to manage, have had fewer side effects, and have required smaller doses, although, because of the wider selection, advanced age, etc., this was difficult to evaluate. Table IV shows the different drugs used in these cases. None of these, however, are included in this study.

TABLE III. THE HYPOTENSIVE DRUGS USED AND THEIR DOSAGES

DRUG	NO. CASES	DOSE PER 24 HOURS
1. Protaveratrine A and B	7*	1.8-7.0 mg.
2. Apresoline	4†	500 -750 mg.
3. Ganglion-blocking drugs:		
a. Hexamethonium chloride	2	3 -4.5 Gm.
b. Pentolinium tartrate	7	600 -1,200 mg.
c. Chlorisondamine	4	200 - 700 mg.
d. Mecamylamine	2	45 - 60 mg.

*Two patients had to be changed to pentolinium.
†Used only as an adjunct to ganglion-blocking drugs.

TABLE IV. GYNECOLOGIC AND POSTPARTUM CASES TREATED

1. Protaveratrine A and B	14
2. Apresoline	7*
3. Ganglion-blocking drugs:	
a. Hexamethonium chloride	12
b. Pentolinium tartrate	10
c. Chlorisondamine	5
d. Mecamylamine	7
Total	48

*Used only as an adjunct to other drugs.

Protaveratrine A and B.—This was found to be the drug that was best tolerated and the one with the fewest side effects. Its only drawback was that in 2 cases even on large doses we were unable to keep the blood pressure down and these cases had to be switched to a more potent ganglion-blocking drug. Several weeks were lost in the switch.

Apresoline.—Our only experience with Apresoline in the oral form has been to supplement ganglion-blocking drugs in 4 cases. Here it appears that

TABLE V. THE EFFECT OF THERAPY ON THE BLOOD PRESSURE (EXPRESSED IN PER CENT OF PRETREATMENT VALUES)

CASES	INITIAL BLOOD PRESSURE	WEEKS ON THERAPY																			
		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1	170/125	100	57	60																		
2	230/120	100	73	67																		
3	160/105	100	64	84	100	84	82	78														
4	200/130	100	65	81	97																	
5	170/100	100	76	76	92	85																
6	190/135	100	74	87	84																	
7	170/110	100	65																			
8	190/130	100	68	61	55	61	87	81	90	94	61	61										
9	210/120	100	80	77	70	80	80	83	83	83	93	70	87	93	70	67	70	83				
10	240/120	100	88	81	72	59	88	84	59	81	75	66	81	88	53	63						
11	170/110	100	92	81	92	88	88	96	100	100	81	81	85	85	100	100	92	92	92	88	119	
12	190/110	100	72	72	86	83	97															
13	220/120	100	69	97	97																	
14	190/120	100	69	74	74	63	75															
15	190/120	100	76	76	75																	
16	190/120	100	80	63																		
17	290/145	100	69	97	74	74	75															
18	200/110	100	81	80																		
19	255/135	100	86																			
20	165/125	100	96	90																		
No. of patients		(20)	(20)	(18)	(13)	(9)	(8)	(5)	(4)	(4)	(4)	(4)	(3)	(3)	(3)	(3)	(2)	(2)	(1)	(1)	(1)	
Average % of pre-treatment values		100	75	78	84	75	84	84	83	89	77	69	84	89	74	77	81	87	92	88	119	

Apresoline has real value. Two of the 4 developed headaches. The only other side effects were leukopenia and hypothermia (following fever) in a case which is reported below.

Ganglion-Blocking Drugs.—Hexamethonium was found to be unsatisfactory because of the small and irregular absorption of the drug, which rendered control of the blood pressure extremely difficult. Mecamylamine is reported to be completely absorbed[3] and Ecolid has a duration of action far exceeding that of any of the other drugs[4]; thus these should be superior to the others but we were unable to tell any difference between these and pentolinium tartrate. None of the gangion-blocking drugs had any detrimental effect upon the fetus.

Blood Pressure Changes During Therapy: It has been noted by many investigators that a hypertensive patient will have her blood pressure at normotensive levels in the hospital on therapy but following discharge on the same dose she will return to the outpatient department with a much higher pressure. This is true even though she has symptoms suggestive of hypotensive levels at home. Freis[5] suggests the visit to the doctor acts as a pressor stimulus that will produce hypertension even though the dose of the hypotensive drug is sufficient otherwise to give a normotensive level. In a group of 32 patients studied by him with both home and office blood pressures, he found the posttreatment diastolic pressure at home to be 20 mm. Hg lower than the pretreatment hospital reading in 27 patients, whereas this degree of improvement was noted in only 6 cases when the posttreatment blood pressure was taken in the office. Smirk[6] also stated that casual blood pressure readings are of little value in the control of dosage. In the graphs presented in this paper it can be readily noted that the inpatient posttreatment blood pressures are quite a bit lower than the outpatient posttreatment blood pressures. Because of the short duration of our management of the hypertensive patient in pregnancy we have not felt it of much value to teach the patient to take her own blood pressure at home, as Schroeder[7] suggests. Of the 20 patients we had only one who followed her own blood pressure at home. Here there was a significantly lower level at home than in the outpatient department. We have relied on symptoms to help adjust the dose where necessary.

In recording blood pressures for evaluation we have used the method of taking the sum of the diastolic plus one-third the pulse pressure. In order to arrive at an average blood pressure change we then calculated the pretreatment blood pressure as 100 per cent and all changes in related percentages. Table V shows the per cent of blood pressure rise or fall for each case during each week of therapy. We have made no attempt to separate the office and hospital blood pressures as the small number of each would have no significance.

Obstetrical Care

Prenatal Evaluation and Care.—All patients were hospitalized initially for studies of hypertension such as eye ground examination, quantitative analysis of proteinuria, urea clearance, blood chemistry determinations, Addis counts, and whatever other studies, such as pyelograms, test for pheochromocytoma, etc., were deemed necessary. If they were selected for therapy they were then kept in the hospital until the dry dosage could be adjusted. After discharge they were followed at intervals of a week or less by the same physician, and a 24 hour quantitative analysis of proteinuria was performed at each visit. Every 4 to 6 weeks they were then rehospitalized for 5 to 10 days, re-evaluated, and the drug dosage readjusted. All of these patients, having refused therapeutic abortion, were extremely anxious to have a living child. They were thus all cooperative patients.

Method of Delivery.—Our plan for delivery of these patients was to set a tentative date at 32 weeks. This is the minimum time that we feel we have a chance to obtain a live infant. At 32 weeks we then evaluated each patient every week, or more frequently, and, depending upon the severity of the hypertension and proteinuria and the size of the infant, we decided when the patient was to be delivered. If proteinuria was in excess of 2 Gm. and the fetus appeared to weigh 1,000 or more grams, we felt delivery should be done by whatever method was easiest for the patient. If the cervix was "ripe" we ruptured the membranes. If not, she was delivered by cesarean section. Nine, or 45 per cent, were delivered by cesarean section, with only one fetal death (due to abruptio placentae). This does not mean, however, that cesarean section is safer, for all fetuses that died in utero were delivered vaginally.

Maternal Complications.—In this group of 20 cases there were no maternal deaths or cerebral vascular accidents, although there was one case of generalized spasm of the cerebral vessels following delivery, which was of short duration and resulted in no apparent damage. Dieckmann[8] reported an incidence of abruptio placentae in chronic hypertensive disease of 9.3 per cent. In these 20 cases abruptio placentae occurred 3 times, an incidence of 15 per cent. In these 3 cases there were 2 fetal deaths. In the case in which the fetus survived there were a partial abruptio and fetal distress at 28 weeks; the infant weighed 825 grams and is completely normal 2 years after delivery. The mother had a blood pressure, renal biopsy, eye ground changes, etc., compatible with malignant hypertension.

Perry and Schroeder[9] reported that 17 out of their 211 patients treated with Apresoline developed collagen disease of various degrees of severity. Their patients had all received the drug for at least 2 months. We had only one bizarre complication. It occurred in a 28-year-old gravida viii, para vii (D. H.), who was referred to us at 31 weeks' gestation with a blood pressure of 230/120, 4 plus proteinuria and 2 plus edema. Hypertension was known to have complicated her last 2 deliveries, but no prenatal care or postpartum care had been received. After several days' bed rest she was placed on hexamethonium chloride and Apresoline, as shown in Fig. 3, reaching a dose of 3.75 Gm. of hexamethonium chloride and 750 mg. Apresoline daily. After 2 weeks' therapy she went into labor spontaneously and was delivered of a 2,220 gram living female infant. On the day of delivery she developed a temperature of 38° C. that rose to 40.2° for the next 3 days, then fell to the 35° range for a few days. The fever was completely unexplained and accompanied by leukopenia as shown in Fig. 4. After the drugs were discontinued both temperature and leukocyte count gradually returned to normal.

From statistics reported by Dieckmann[10] from both Chicago and New York Lying-In Hospitals it appears that the patient with vascular disease before pregnancy is made worse by each pregnancy. We cannot state from so few cases that hypotensive drugs prevent this damage. The drugs have certainly given us courage to carry some women through pregnancies which we would heretofore have terminated.

Fetal Complications.—Of the 20 patients, 14, or 70 per cent, left the hospital with live infants. In 1953 Dieckmann[8] reported that only approximately one third of women with severe chronic hypertensive disease leave the hospital with live infants; hence on the surface we appear in this small series to have improved our fetal survival by 100 per cent. He also reported an abortion rate of 18.2 per cent in cases of severe hypertension. We had no abortions, but in only 3 of the 20 cases was therapy started before the twentieth week. Most of our hypertensive patients did not report for prenatal care until they had passed the stage when abortions are most prevalent.

Table VI shows the fetal loss by weight. Seventy per cent of the infants delivered weighed between 400 and 2,500 grams. In this group we had a fetal mortality of 42.5 per cent; there were no losses in those above 2,500 grams. If we consider only those from 1,000 to 2,500 grams, we have 10 cases

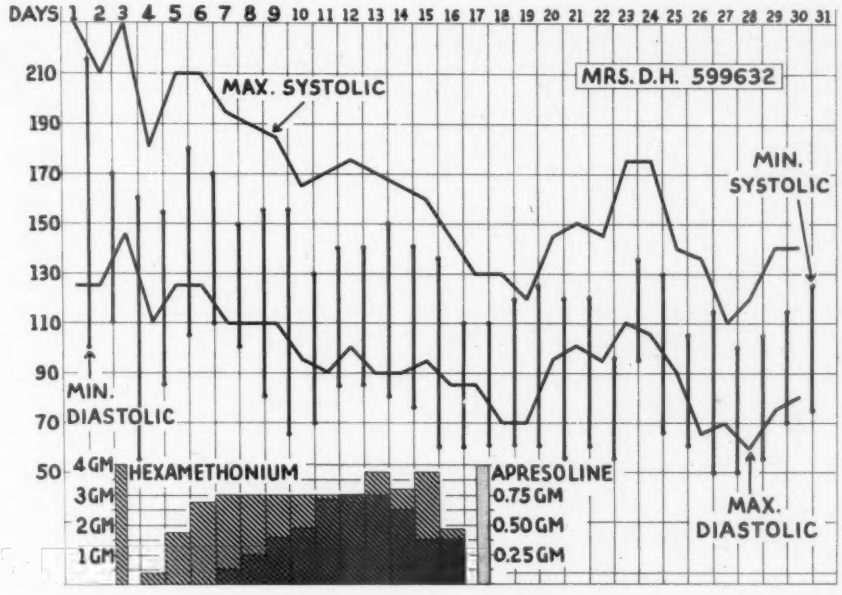

Fig. 3.—Blood pressure response to combination of hexamethonium and Apresoline therapy.

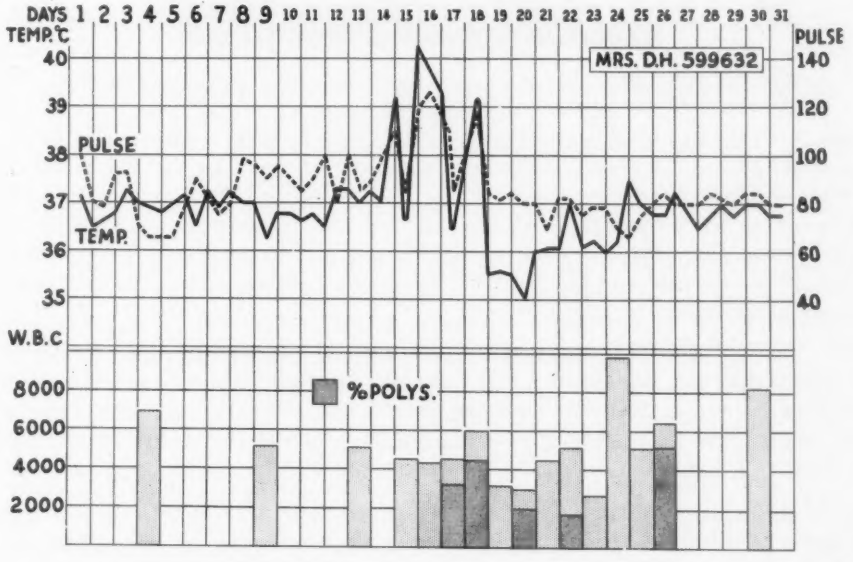

Fig. 4.—The days correspond to Fig. 3. Temperature and white blood count shown.

with a fetal loss of 30 per cent. In Dieckmann's report of 1953[8] (at which time we were not using hypotensive therapy on a long-term basis) he showed that in severe hypertensive disease there was an incidence of prematurity of 31.9 per cent with a fetal loss of 35 per cent. In the light of these facts we do not feel that our fetal survival is much greater than it was prior to hypotensive

drug therapy. Two of the 3 fetal deaths of infants weighing over 1,000 grams might have been prevented if the patients had not been on hypotensive therapy.

TABLE VI. PERINATAL MORTALITY

FETAL WEIGHT (GRAMS)	TREATED CASES	PERINATAL LOSS	
		NO.	%
400+	20	6	30
1,000+	16	3	18.7
1,500+	13	2	15.4
2,000+	9	0	0
2,500+	6	0	0
400-2,500	14	6	42.8
1,000-2,500	10	3	30

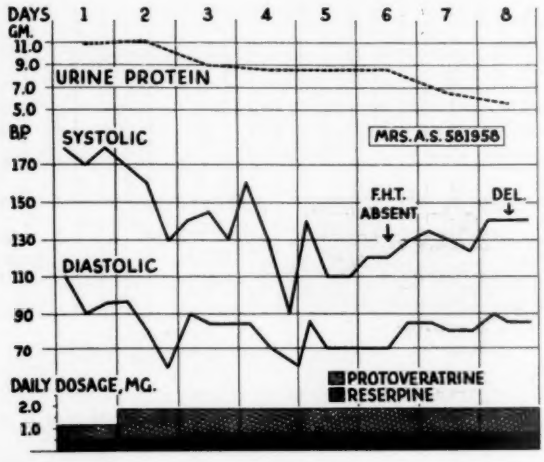

Fig. 5.—Case of chronic glomerulonephritis treated with protoveratrine.

Case 1.—This was a 38-year-old gravida iii, para 0, with known hypertension for 20 years (systolic pressure in excess of 200 mm. Hg). When first seen she had a blood pressure of 300/150, with very little proteinuria. She was placed on Inversine and carried with a blood pressure of around 200/120. As she had very little proteinuria we attempted to carry her further than good obstetric sense would indicate. At approximately 36 weeks she developed abruptio placentae and was delivered by cesarean section of a 1,700 gram infant that died shortly after birth.

Case 2.—The other case was that of a 38-year-old gravida iv, para ii, with a history of hypertension late in pregnancy. At 32 weeks she developed severe hypertension which was lowered on Ecolid. One week later she had proteinuria, 5 Gm. in a 24 hour specimen, but her pregnancy was not terminated. The next week she was delivered of a stillborn, 1,575 gram female infant.

Had these two patients not been on hypotensive therapy we probably would have terminated their pregnancies earlier. Hence we feel that one must not be lulled into a false sense of security just because the blood pressure has been lowered. The infant will still die in utero in these cases even though the blood pressure is nearly normal. The other 4 cases associated with fetal loss are described as follows:

Case 3.—This patient was a 24-year-old gravida i, para 0, with severe hypertension known before pregnancy. She was first seen and placed on hexamethonium chloride at 22

weeks' gestation. The drop in blood pressure was satisfactory but at 26 weeks her physician stopped medication because of severe side effects. At 28 weeks the blood pressure and proteinuria became so high that her pregnancy was terminated by hysterotomy and a 1,055 gram male infant obtained, that died of a sort of hyaline membrane disease.

Case 4.—This 28-year-old gravida ii, para 0, had a sympathectomy performed during her first pregnancy, only to deliver a stillborn macerated fetus at 25 weeks. Before the start of the second pregnancy this patient was taking pentolinium tartrate. The blood pressure remained near normal but at 26 weeks she was delivered of a macerated 780 gram male infant.

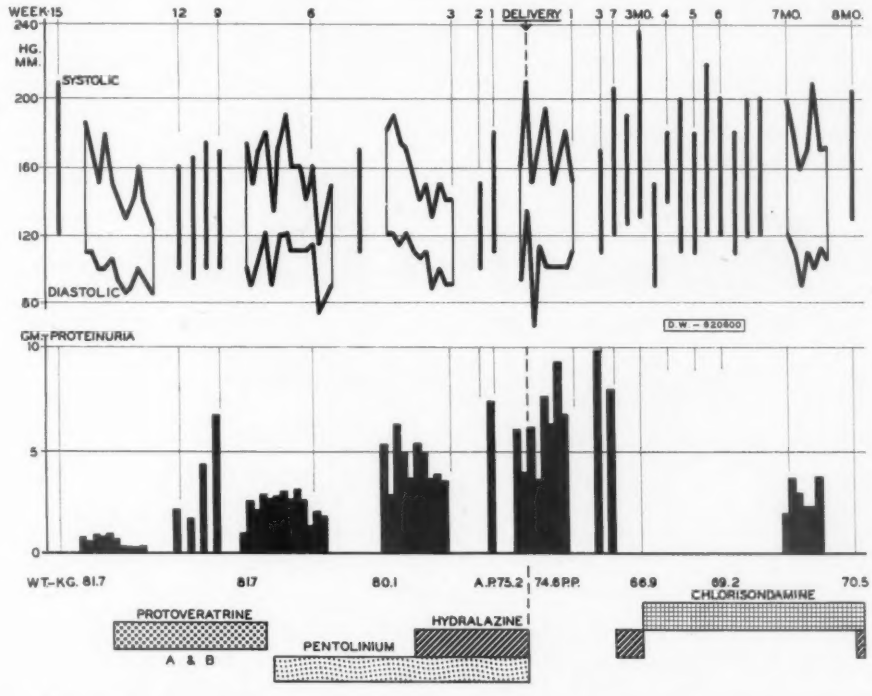

Fig. 6.—Essential hypertension treated with protoveratrine A and B, then changed to pentolinium and 1-hydrazine. Vertical lines represent outpatients' blood pressure readings.

Case 5.—Mrs. A. S. was a 44-year-old gravida ii, para 0, whose first pregnancy was terminated at 26 weeks because of a sudden increase in proteinuria to 10 Gm. per 24 hours, and hypertension of 205/110. This pregnancy was essentially normal except for proteinuria of 0.5 Gm. per 24 hours until again at 26 weeks she was seen with a hypertension of 180/110, 2 plus edema, and 11 Gm. of protein. As can be seen in Fig. 5, she was placed on protoveratrine and reserpine, which resulted in a normal blood pressure, but the proteinuria remained at a dangerous level and on the sixth day of therapy the fetal heart tones disappeared and 2 days later she was delivered of a 650 gram stillborn infant. A diagnosis of chronic glomerulonephritis was established by renal biopsy.

Case 6.—Mrs. H. W., a 34-year-old gravida iv, para 0 (last abortion 13 years previously), was first seen when she was 12 weeks pregnant. She had rather large myomas and 4 years before this pregnancy a gynecologist at another hospital had admitted her for operation, which was not done because of severe hypertension. When she was first seen her blood pressure was 210/120. As seen in Fig. 6, it was very difficult to keep her blood pressure down. She was first placed on protoveratrine A and B but even 6 mg. daily failed to control the blood pressure; hence, she was placed on a pentolinium and Apresoline combination which

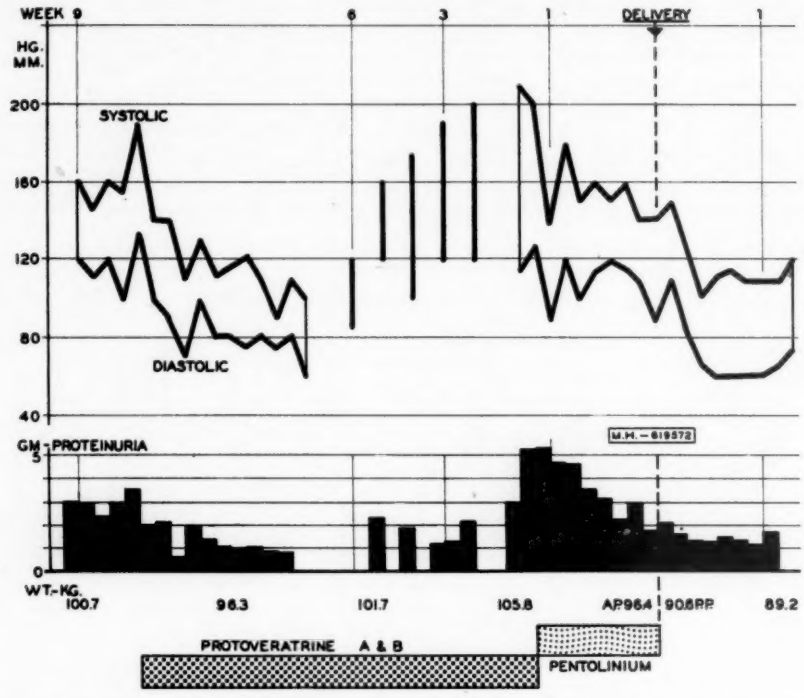

Fig. 7.—Essential hypertension. Vertical lines represent outpatients' blood pressure readings.

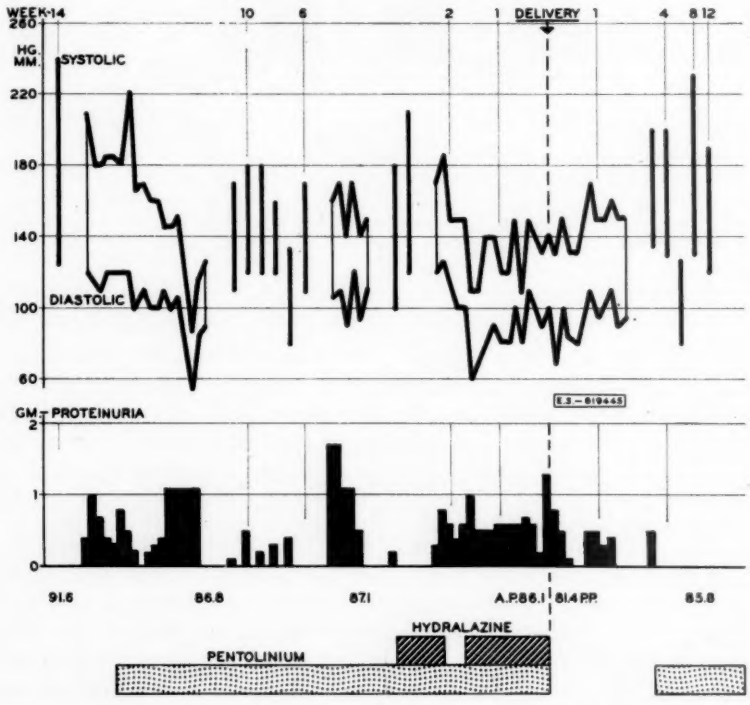

Fig. 8.—Essential hypertension. Vertical lines represent outpatients' blood pressure readings.

reached daily doses of 2,400 and 600 mg. respectively, before the blood pressure was lowered. At 28 weeks she was admitted with complete abruptio placentae and a dead fetus. Labor was then induced and she was delivered of a 860 gram stillborn female infant. Following delivery her blood pressure has remained high and somewhat resistant to therapy.

We are unable to state definitely that we have obtained a higher fetal salvage with hypotensive drug therapy, but we can state that we have seen no harmful effects upon the fetus from the drug itself. All of the infants on ganglion-blocking drugs have been examined carefully by the pediatric department for evidence of paralytic ileus but none has been detected.

Ten of 20 patients had or developed proteinuria in excess of 2 Gm. per 24 hours. In these the fetal mortality was 40 per cent, compared to 20 per cent in the group that had less than 2 Gm. per 24 hours. This is comparable to the figures given by Dieckmann and Kramer[11] in 1942, who reported a higher fetal loss as proteinuria became greater.

The following 2 cases show some of the difficulties in maintaining and managing a patient on hypotensive therapy.

Case 7.—Mrs. H. was first seen at approximately 30 weeks' gestation with moderate hypertension and proteinuria (Fig. 7). The proteinuria improved on bed rest but the hypertension remained moderate, and so she was placed on protoveratrine. The pressure abated for some 3 weeks, at which time it began to rise in spite of the increased dosage. She was then placed on pentolinium and carried until approximately 37 to 38 weeks, at which time she was delivered by cesarean section of a viable, 3,010 gram male infant.

Case 8.—Mrs. E. S., a 36-year-old gravida i, para i, was very anxious to have a baby. She was first seen at 20 weeks' gestation with marked hypertension but only a moderate proteinuria (Fig. 8). She was carried satisfactorily on pentolinium except for repeated increases in dosage; for the last 3 weeks the pentolinium had to be supplemented with Apresoline. At 35 weeks it was felt that the infant was viable and she was delivered by a cesarean hysterectomy (because of myomas) of a 1,700 gram viable infant.

Conclusions

During five and one-half years of careful searching for suitable cases of chronic hypertensive disease complicated by pregnancy, we were able to find 20 out of 1,100 cases of toxemia with which to evaluate the various hypotensive drugs. Twenty cases are by far too few to provide any statistically significant data, but we feel that they have helped us to evaluate what if any value can be derived from a lowered blood pressure in this type of case. There was no decrease in quantitative proteinuria, nor was there a decrease in the incidence of abruptio placentae. There was a decrease in perinatal mortality, but this could be easily explained by better prenatal care and cooperation of the patients. It is certainly logical to assume that cerebral hemorrhage, which is a common cause of death in hypertensive patients, would be lower in a treated group. It is also possible that damage to the vascular system might be averted. The only detrimental effect that might be attributed indirectly to hypotensive drug therapy is that the obstetrician might be lulled into a false sense of security by the lowered blood pressure curve. We doubt very seriously that any drug will ever replace good obstetrical judgment. One should not attempt to carry these patients any further than necessary in order to obtain a viable infant. With our present knowledge, we still feel these patients with long-term hypertension that does not respond to bed rest should be offered therapeutic abortion if seen early in pregnancy.

We wish to thank the following pharmaceutical companies for supplying the drugs used in this paper:

1. Warner-Chilcott Laboratories—hexamethonium chloride (Methium).
2. Pitman-Moore Company—protoveratrine A and B (Veralba).
3. Ciba Pharmaceutical Products, Inc.—hydralazine hydrochloride (Apresoline) and chlorisondamine chloride (Ecolid).
4. Merck Sharp & Dohme—mecamylamine hydrochloride (Inversine).
5. Wyeth Laboratories, Inc.—pentolinium tartrate (Ansolysen).

References

1. Kellar, R. J.: J. Obst. & Gynaec. Brit. Emp. **62**: 683, 1955.
2. Dieckmann, William J.: The Toxemias of Pregnancy, St. Louis, 1952, The C. V. Mosby Company.
3. Moyer, J. H., Ford, R., Dennis, E., et al.: A. M. A. Arch. Int. Med. **98**: 187, 1956.
4. Grimson, Keith S.: J. A. M. A. **158**: 359, 1955.
5. Freis, Edward D.: Med. Ann. District of Columbia **23**: 1, 1954.
6. Smirk, F. H., and Alstad, K. S.: Brit. M. J. **1**: 1217, 1951.
7. Schroeder, Henry A.: Hypertensive Diseases, Philadelphia, 1953, Lea & Febiger.
8. Dieckmann, William J.: S. Clin. North America **33**: 27, 1953.
9. Perry, H. M., and Schroeder, H. A.: J. A. M. A. **154**: 670, 1954.
10. Dieckmann, William J., Smitter, A. B., and Rynkiewicz, L.: Am. J. Obst. & Gynec. **64**: 850, 1952.
11. Dieckmann, William J., and Kramer, S.: J. A. M. A. **120**: 590, 1942.

Discussion

DR. STANLEY T. GARBER, Cincinnati, Ohio.—Before discussing this specific paper please permit me to correct briefly a common misconception. We aim in the employment of hypotensive drugs not simply to lower blood pressure—which is merely a gauge—but to decrease peripheral resistance and improve the circulation.

Simply expressed, blood pressure is maintained by several factors which include: cardiac output, effective circulating blood volume, viscosity of the blood, and peripheral resistance.

Peripheral resistance or arteriolar resistance is the factor with which we are primarily concerned in the hypertensive diseases of pregnancy. Hypotensive drugs are primarily aimed at reducing this. Peripheral resistance is made up of several components, namely: an intrinsic component, inherent resistance or elasticity of the vessel wall; a neurogenic component, controlled by the autonomic nervous system; and a humoral (nonneurogenic) component, comprising all nonintrinsic and nonneurogenic factors.

There are several basic physiologic patterns which may account for the hypertension seen in various clinical conditions. In one form the elevated blood pressure seems to be maintained by the resistance intrinsic in the vessel wall as in the so-called "pipe stem" vessels of the aged. In one form the elevated blood pressure seems to be maintained primarily by humoral mechanisms, e.g., acute glomerulonephritis, pre-eclampsia-eclampsia of pregnancy, and certain cases of essential hypertension. In another group neurogenic factors seem to play the primary role, e.g., patients with essential hypertension whose pressure consistently falls to normal range in response to autonomic blockade. Incidentally the blood pressure in normal pregnancy is maintained chiefly by neurogenic factors. Many cases of essential hypertension fall somewhere between the latter two groups with humoral and neurogenic factors showing varying degrees of importance. Emotional tensions play an important role in some. In others, changes in the sodium and water balance may vary the humoral and neurogenic components greatly, even from day to day.

A brief review of vasodepressor drugs is in order, since they vary considerably in the mode of action and the site at which this action takes place. For convenience they may be divided into four main groups:

Group A.—The veratrum alkaloids, phthalazine compounds (Apresoline) and *Rauwolfia serpentina.* This group is believed to act on the central nervous system at the level of the hypothalamus or on the vasomotor center. Some impulses are mediated through the vagus

system. The antihypertensive effect of these drugs is directed primarily against "humoral" hypertensive stimuli. Good motor coordination is retained even with the use of Rauwolfia, which brings about sedation and reduced emotional response.

Group B.—Spinal anesthesia and ganglion-blocking agents (tetraethylammonium chloride, or TEAC, the methonium series, penta, hexa, etc., thiophanium compounds such as Ro2-222 or Arfonad, Pendiomide and numerous other derivatives). Spinal anesthesia blockades vasoconstrictor impulses in the subarachnoid space, whereas autonomic blockading agents act at the ganglionic level. Because the response is the same, they are considered together. These agents blockade the vasomotor impulses to both the arteriolar and the venous systems, thus producing venous pooling. Postural hypotension results, thereby creating most undesirable side effects. The most hypotensive effect is exerted against vasopressor impulses of neurogenic origin as in normal pregnancy and in some forms of essential hypertension associated with pregnancy. Toxemic patients show very little effect.

Group C.—Peripherally acting drugs (Priscoline, Dibenzyline, and Dibenamine). These drugs act at the nerve endings close to the neuromuscular junction. Their effect is transient and they are not too practical because of side effects.

Group D.—Adrenolytic substances (Regitine and benzodioxane). These drugs counteract circulating epinephrine or its related amines and are used in diagnostic tests for peochromocytoma. Circulating epinephrine plays no role in maintenance of blood pressure in either normal term or toxemic pregnancy.

Our experience with the hypertensive diseases and pregnancy comes from the Cincinnati General Hospital. Seventy per cent of the obstetric admissions are Negro patients. Of the nearly 5,000 admissions a year on this service about 500, or approximately 10 per cent, have some form of hypertension. Of these, about 50, or 10 per cent, a year have essential hypertension with or without superimposed pre-eclampsia or eclampsia. In this group we have found the Rauwolfia (Serpasil) group of hypotensive drugs more satisfactory than the autonomic blockading agents. About 10 per cent of the patients develop sniffles but other side effects are minimal. Where there is superimposed pre-eclampsia-eclampsia we employ in addition the Veratrum-Apresoline drugs which we feel are most beneficial.

As the authors have pointed out, there is no substitute for bed rest. They failed to credit the importance of a diet restricted in sodium and high in protein, together with desalting by means of Diamox, magnesium sulfate, and adequate fluid intake. All of these are best controlled under hospital conditions.

Their warning about being lulled into a false sense of security with some patients under the influence of hypotensive drugs is timely. This has happened to us.

I am at a loss to find the criteria by which the selection of hypertensive patients was made by the authors. Was it on the basis of past history, hypertension before pregnancy, or, as I suspect, on blood pressure over 180/110 during pregnancy? Was any distinction made between chronic hypertension and hypertension with superimposed pre-eclampsia-eclampsia? We feel that the prognosis, complications, fetal mortality, etc., are greatly enhanced in the latter group. Likewise, the response to hypotensive drugs varies in this group.

I am amazed at the number of therapeutic abortions performed for essential hypertension at the Chicago Lying-in Hospital. We expect superimposed pre-eclampsia-eclampsia in only 50 per cent of our patients with essential hypertension. The amazing thing to me is that in the other 50 per cent we can count on no aggravation of the hypertension and occasional improvement during the pregnancy. The fetal mortality in the entire group is increased, of course. In the past 6 years on the obstetric service we have not performed a single therapeutic abortion. In no case where it was considered did a death result. We do offer tubal ligation following delivery, however, in proved cases of chronic hypertension and renal disease.

PREGNANCY FOLLOWING TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA WITH CORTISONE*

ROBERT B. WILSON, M.D., AND F. RAYMOND KEATING, JR., M.D.,
ROCHESTER, MINN.

(From the Section of Obstetrics and Gynecology, and the Section of Medicine, Mayo Clinic and Mayo Foundation†)

THE congenital adrenogenital syndrome is the striking consequence of pathologic secretion of androgens by an abnormal and hyperplastic adrenal cortex beginning in intrauterine life. Interest in this bizarre condition was increased by the finding of Wilkins and co-workers[1, 2] in 1950 and 1951 that cortisone therapy effectively abolished the excessive excretion of 17-ketosteroids as well as the clinical evidence of excessive production of androgen, and permitted the emergence of normal ovarian function, as manifested by regular menstruation. Soon after, Bartter and co-workers[3] reported similar results. The study of pregnancy following cortisone therapy in patients with this condition should therefore be of especial interest.

We have had the fortunate experience of observing 2 women with congenital adrenogenital syndrome who, after responding characteristically to adrenal steroid therapy, conceived and gave birth to live normal infants at term. Except for the report of the patient of Yamashita and Kozakae,[4] we have found no reports of live birth at term of normal infants in association with this condition.

In 1937[5] and 1938[6, 7] Ingle and co-workers reported that cortin administered to rats caused atrophy of the adrenal cortex, and they presented evidence to show that the atrophy was due to suppression of the adrenotropic function of the pituitary. It was not until 1950[8] and 1951 that Sprague and co-workers[9] reported that similar suppression of the adrenal cortex occurred in human beings treated with cortisone. They warned that endogenous adrenal cortical function might be depressed during and for an interval after administration of this hormone. In 1951 and 1952 Wilkins and co-workers[2, 10-12] reported the successful use of cortisone in the treatment of patients with congenital adrenogenital syndrome. In attempts to elucidate the abnormal physiology involved, Bongiovanni and co-workers[13] noted the regular presence of pregnanetriol in the urine of these patients and observed that pregnanetriol is the urinary excretion product of 17-hydroxyprogesterone presumed to be the immediate precursor of 17-hydroxycorticosterone (compound F).

These findings suggest that the essential pathologic physiology in this syndrome is an inborn inability of the adrenal cortex to synthesize 17-hydroxycorticosterone. The absence of the suppression normally furnished by

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†The Mayo Foundation, Rochester, Minn., is a part of the Graduate School of the University of Minnesota.

17-hydroxycorticosterone is followed by hypersecretion of pituitary adrenocorticotropin, and this in turn causes the adrenal cortex both to undergo hyperplastic changes and to produce androgenic steroids in excess. These, however, do not suppress endogenous adrenocorticotropin, and the vicious cycle that results when this occurs in utero may produce the clinical picture of pseudohermaphroditism in females or macrogenitosomia praecox in males.

Atypical and mild forms of the adrenogenital syndrome have been found by some authors to respond successfully to treatment with cortisone. Jones[14] and Jones[15] and also Greenblatt[16, 17] and their co-workers reported that a number of patients with clinical and laboratory evidence of increased adrenal androgenic function ovulated, became pregnant, and were delivered of normal children when treated with cortisone. In patients with congenital adrenogenital syndrome treated with cortisone, return of menstruation has been almost universal, but the occurrence of pregnancy in such patients has to date been rarely reported. Yamashita and Kozakae[4] have reported upon one patient with congenital adrenogenital syndrome who was treated with cortisone and was delivered at term. de Alvarez and Smith[18] described 2 such patients, one of whom became pregnant but aborted at the fourth month. Wilhelm and Marks[19] reported 2 cases of adult adrenogenital syndrome. One patient was delivered of 2 children after partial adrenalectomy. The other, after cortisone treatment, was delivered of a premature infant (30 weeks) that died neonatally, on the third day.

Report of Cases

CASE 1.—A healthy white woman, aged 29 years, was first seen at the Mayo Clinic in March, 1955, because of infertility. The patient recalled some vaginal staining at the age of 17, which did not require a pad. Such staining had recurred from time to time. She had been married 3½ years previously but no pregnancies had occurred. Physical examination revealed a receding hair line, thin scalp hair, mild facial and bodily hirsutism, prominent jaw, minimal development of the breasts, and a masculine muscular habitus. Her height was 60 inches, her weight 122 pounds, and her blood pressure 114 mm. of mercury systolic and 72 diastolic. Pelvic examination showed normal pubic hair and considerable enlargement of the clitoris; her mother stated that this enlargement had been present since birth. There were no other vulvar abnormalities, the vagina was of normal depth, and the uterus and ovaries were palpably normal. The tubes were patent. No tissue was obtained when an endometrial biopsy was done.

Routine laboratory examinations gave negative results. The sella turcica appeared normal on x-ray examination. The basal metabolic rate was minus 1 per cent. Urinary excretion of 17-ketosteroids measured 19.3 mg. in 24 hours; a second determination was 27.7 mg. in 24 hours. Subsequent assay data are summarized in Table I. An excretory urogram on May 10 was of normal appearance. A diagnosis of female pseudohermaphroditism (congenital adrenogenital syndrome) was made.

Shortly thereafter the patient moved to another community, but we were able to collaborate with her local physicians in her management. Hydrocortisone therapy was started in May, 1955 (Table I), and was continued with adjustment in dosage as indicated by determinations of 17-ketosteroids. Menstruation began in May, 1955, and occurred regularly and normally each month. No menses occurred after October, 1955, and a pregnancy test in December, 1955, gave positive results. Hydrocortisone therapy was continued during pregnancy in a dosage (Table I) that seemed to maintain excretion of urinary 17-ketosteroids between 8 and 13 mg. each 24 hours. Following a normal labor the patient was spontaneously delivered of a normal female infant at term on July 6, 1956.

After delivery the patient stopped hydrocortisone therapy of her own volition. As indicated in Table I, this did not result in any immediate increase of 17-ketosteroids. Following parturition the menstrual function returned, with a cycle of 21 to 28 days. However, the patient has had no menses since June, 1957. The first determination of 17-ketosteroids thereafter, on August 17, 1957, was somewhat greater than it was previously (12.3 mg. in 24 hours) but this was not thought to be great enough to require cortisone therapy. A pregnancy test in August, 1957, gave negative results. At present we are in doubt as to whether the patient is again pregnant or whether the original abnormality has returned.

TABLE I. LABORATORY AND TREATMENT DATA IN CASE 1

DATE	17-KETOSTEROIDS (MG. IN 24 HOURS)	CORTICOIDS (MG. IN 24 HOURS)
1955.—		
4/4	19.3	1.15
4/7	27.7	
5/10	28.1	0.57
	ACTH test, 40 units intramuscularly on 5/11 and 5/12	
5/11	57.8	0.93
5/12	32.3	1.00
	Cortisone, 50 mg. daily for 3 days then every other day	
5/14	40.8	0.69
5/26	4.4	0.74
6/1	Hydrocortisone acetate, 250 mg. intramuscularly repeated approximately every 2 weeks	
6/15	18.5	0.93
6/22	11.3	0.67
7/17	17.7	0.81
7/25	20.0	0.81
8/17	10.1	0.77
8/24	11.9	0.54
10/1	10.9	1.08
10/11	15.9	0.68
12/17	Pregnancy test positive	
12/29	11.2	
	Hydrocortisone, 250 mg. intramuscularly every 2 weeks	
1956.—		
4/13	12.7	0.87
4/13	Hydrocortisone, 250 mg. intramuscularly every 2 weeks	
7/6	Delivery	
7/6	Cortisone therapy discontinued	
8/27	2.2	1.13
10/11	2.2	0.39
11/27	8.2	0.66
1957.—		
1/7	7.5	0.68
4/2	5.9	0.77
6/18	12.7	1.09
8/17	12.3	0.51

The clinical features of congenital virilization in this patient were much less conspicuous than in the second case, but these features together with a definite developmental history and a characteristic pattern of hormone excretion were regarded as affording a decisive diagnosis.

The response to the administration of adrenocorticotropin was characteristic of the adrenal hyperplasia of the adrenogenital syndrome (Table I): excretion of 17-ketosteroids increased to 57.8 mg. per 24 hours without significant change

in the excretion of corticoids. Such marked increase is not customarily seen in patients with normal adrenal function or in those with adrenal tumor. The prompt return of the excretion of 17-ketosteroids to normal, associated with the appearance of menstrual function upon initiation of hydrocortisone therapy, constitutes further evidence of adrenogenital syndrome.

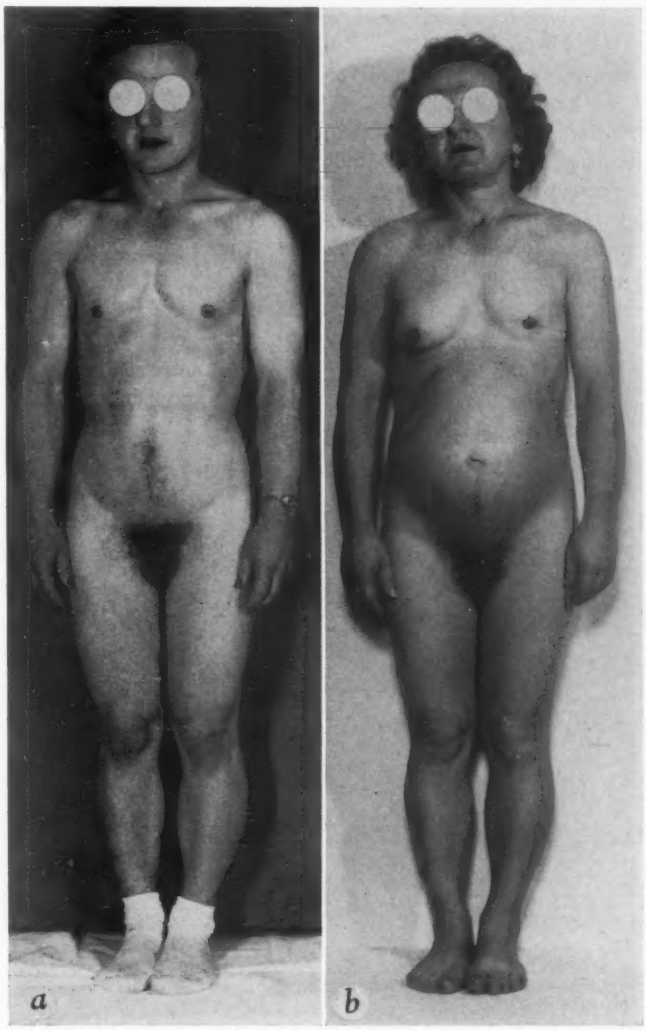

Fig. 1.—Case 2. *a*, May 30, 1946. The masculine physique of this patient is quite striking. There is no development of the breasts. *b*, Feb. 13, 1957. Appearance during the seventh month of gestation. The deformity of the left breast is due to surgical removal of a large area of cystic mastitis.

The dose of cortisone was not changed during pregnancy, since urinary excretion of 17-ketosteroids remained within the normal range, although not as low as the 8 mg. in 24 hours that Wilkins and co-workers recommended. The patient was prepared for delivery by the intramuscular administration of 200 mg. of cortisone at the onset of labor. It was planned to repeat this dose every 8 to 12 hours during labor and to give additional hydrocortisone intravenously

as needed to maintain the blood pressure or treat clinical evidence of adrenal insufficiency. The patient's labor was normal in all respects, however, and such measures were not required. A thorough examination of the infant revealed no abnormalities.

CASE 2.—A white woman, aged 22 years, when first seen at the Mayo Clinic, in May, 1946, complained of a growth on the vulva and that she had never menstruated. Physical examination disclosed a very masculinized woman (Fig. 1,*a*). The patient's height was 61 inches, her weight 115 pounds, and her blood pressure 120/70. Marked growth of hair on face, arms, and legs was present and the voice was husky. The "growth" on the vulva was a clitoris, 4 to 5 cm. long (Fig. 2,*a*), the vagina was deep and narrow with a small cervix in the vault, the uterus was very small, and nothing was felt in the adnexa. At this time (1946) the results of routine laboratory studies were within normal limits, the basal metabolic rate was plus 13 per cent, the value for urinary estrogens, 53 rat units in 24 hours, and the value for urinary pituitary gonadotropin, zero. The excretion of 17-ketosteroids was 86 mg. per 24 hours. A diagnosis of classic pseudohermaphroditism associated with congenital adrenogenital hyperplasia was made. Surgical exploration with consideration of subtotal adrenalectomy was suggested, but the patient elected to defer this.

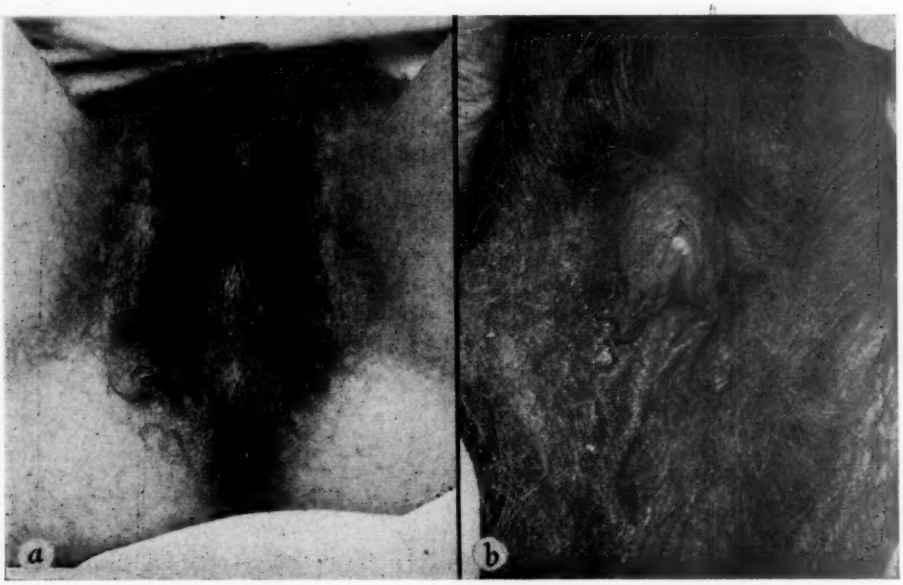

Fig. 2.—Case 2. *a*, May 30, 1946. External genitals with prominent clitoris. *b*, Feb. 13, 1957. External genitals show little change in 7 years. This photograph shows the enlarged clitoris more clearly.

The patient returned in January, 1955, having attained the age of 31 and having been married. Complaints suggestive of disease of the gall bladder were voiced. Her appearance and the physical findings had not changed appreciably since the first visit in 1946. The clitoris was still enlarged as before with the uterus remaining small. The patient had had no menstrual periods.

Treatment with adrenal steroids was started on Jan. 15, 1955. Therapy and assay data are summarized in Table II. The patient experienced her first menstrual period in March; thereafter menses occurred at intervals of 26 days and lasted 6 or 7 days until a "last menstrual period" occurred on Aug. 15, 1956. When she was seen on Nov. 30, 1956, intrauterine pregnancy was obvious.

The prenatal course was uneventful in nearly all respects. The gain in weight was minimal, from 123½ pounds in November, 1956, to 129½ pounds at term. There was no increase in blood pressure at any time, and the results of urinalysis were consistently negative. The patient's appearance at the seventh month of gestation and the appearance of the external genitals are shown in Figs. 1,*b* and 2,*b*. The pelvis both clinically and roentgenographically was contracted and it was thought that a cesarean section would probably be necessary.

The patient went into labor spontaneously on May 14, 1957, at the thirty-ninth week of gestation. The membranes ruptured at the onset of labor. The cervix dilated to 6 cm., with the presenting vertex at station minus 2. There was no further cervical dilation or descent of the vertex during the next 4½ hours of labor in spite of excellent uterine contractions. Consequently, with the patient under local anesthesia, a low cervical cesarean section was done with delivery of a normal female infant who weighed 2,890 grams. The postoperative course was uncomplicated.

This patient also discontinued cortisone therapy when she left the hospital. No withdrawal symptoms were experienced. She noticed a scanty brownish discharge on July 27, and experienced a seemingly normal menstrual period from Aug. 10 to 15, 1957. During the month of September, 1957, scant daily bleeding occurred but we have had no recent opportunity to examine the patient.

TABLE II. LABORATORY AND TREATMENT DATA IN CASE 2

DATE	17-KETOSTEROIDS (MG. IN 24 HOURS)	TREATMENT
5/31/46	86.0	None
1/15/55	18.1	Cortisone, 50 mg. in 24 hours
2/15/55	19.4	Cortisone, 75 mg. in 24 hours
3/15/55	5.4	No change
8/19/55	6.4	Hydrocortisone, 200 mg. intramuscularly every 2 weeks
10/22/55	16.5	Hydrocortisone, 375 mg. intramuscularly every 2 weeks
3/14/56	10.7	No change
7/10/56	2.9	No change
10/ 9/56	11.5	No change
11/ 7/56	8.0	No change
11/30/56	—	Prednisone, 5 mg. every 12 hours
1/26/57	6.3	No change
3/27/57	8.3	No change
5/14/57	11.8	No change
	Delivery	Cortisone therapy discontinued
6/29/57	8.6	
	Corticoids 0.56	
8/28/57	16.6	
	Corticoids 0.41	

This patient's response to therapy was excellent as soon as an adequate amount of cortisone was given. No particular difficulties were encountered when the type of cortisone was changed, first to hydrocortisone by intramuscular injection and then to prednisone by mouth. During the 17 months of therapy no signs of hypercortisonism were noted.

The management after the onset of labor included intramuscular administration of 200 mg. of cortisone on admission to the hospital. This dose was repeated twice before cesarean section and on the fifth, sixth, and seventh postoperative days. No cortisone was required intravenously although it was available had there been any evidence of an adrenal crisis.

Comment

These 2 cases illustrate marked quantitative differences in the severity of virilization, but careful comparison of symptoms, response to treatment, and patterns of hormone excretion provides an adequate basis for considering that they represent degrees of the same disorder. The congenital adrenogenital syndrome also varies greatly from case to case with regard to the degree of genital deformity, depending upon the time in intrauterine life at which abnormal adrenal function begins. When this occurs before the external genitals are differentiated (about the third or fourth month of gestation) anatomic abnormalities of the external genitals generally result. In extreme cases the vagina may be reduced to an offshoot of the urethra and the external genitals may resemble those of a male with cryptorchid testes and hypospadias. The designation "female pseudohermaphroditism" is most appropriate in cases of this sort but it should be emphasized that the endocrine disorder is the same whether such anatomic abnormalities are present or absent. Both patients here presented had anatomically normal female genitourinary tracts and both were raised as females. From a therapeutic standpoint they posed no particular problem once adrenal suppression had been effected with cortisone. However, patients in whom early onset of virilization has produced irreversible and anomalous genital changes usually require more than suppressive treatment alone. Provided the patient is recognized as a female infant at birth and is raised in the psychological and cultural pattern of females, adequate treatment may also require some plastic surgical procedure to establish normal anatomic relationships. No instance has yet been reported of pregnancy following treatment of such complete pseudohermaphrodites. There is, however, no theoretical reason why it might not occur.

The management of patients with adrenogenital syndrome requires periodic assay of urinary 17-ketosteroids as a guide to the regulation of cortisone dosage necessary to suppress production of corticotropin. Periodic evaluation of blood electrolytes is usually unnecessary except in occasional instances (usually male children) in which there is concomitant adrenal insufficiency similar to that of Addison's disease. Protecting the patient with large quantities of cortisone prior to delivery or any other stress should be emphasized. The nature of the metabolic defect in the adrenal cortices makes it improbable that they can protect the patient against stress in a normal way. We have followed the practice of treating these patients before and following delivery or surgical treatment in the same manner as patients with Addison's disease. Cortisone, 200 mg., is given intramuscularly two or three times within the 36 hours preceding the event to provide a high level of circulatory steroid at the time of stress; blood pressure levels and parenteral fluid therapy are closely watched subsequently, and further replacement therapy is dictated by the course of the patient.

de Alvarez[18] theorized that an increase in 17-ketosteroids from 5 to 13 mg. in 24 hours reflected an increase in adrenal androgen sufficient to interfere with normal ovarian function and contributed to the abortion that occurred in his patient. Jones and Jones[14] reported that abortion occurred in half of their patients. We noticed fluctuation in excretion of 17-ketosteroids as great as or greater than this (Tables I and II) in these 2 patients on a number of occasions, yet neither experienced any symptoms suggestive of abortion. Marked fluctuations should probably be prevented when possible, but this experience suggests that moderate fluctuation in urinary 17-ketosteroids is not harmful and we have considered it unnecessary to alter the dose of cortisone with every minor change in urinary 17-ketosteroids.

Should it prove possible that a patient might maintain pregnancy despite abnormal levels of adrenal androgen, the question might arise as to the possible effects of such levels upon the fetus. Theoretically, if one assumes that androgens may penetrate the placental barrier, one might anticipate virilization in the fetus analogous to that of a fetus that itself had the adrenogenital syndrome, that is, macrogenitosomia praecox in a male or pseudohermaphroditism in a female, provided the abnormal levels were present prior to the fourth month of gestation. Such children might not necessarily have the adrenogenital syndrome, but might nevertheless bear stigmas of it from temporary exposure to virilizing influences in utero, which in females at least could prove disastrous. It is therefore of particular interest that both babies reported here were females, and both were entirely normal in all respects. This indicates at least that the levels of androgen secretion in these cases were insufficient to produce harmful effects upon the genitourinary development of these girl babies.

The course of the patients after delivery and following unplanned cessation of therapy has been of considerable interest. In the first patient, normal menstrual function returned and the values for urinary 17-ketosteroids have remained within normal range. We are currently in doubt whether she has become amenorrheic because of another pregnancy or because of a return of excess adrenocortical androgens. In any event, for approximately 1 year following delivery the level of 17-ketosteroids has remained satisfactory. Since only 4 months have elapsed since delivery of the second patient, it is not possible to assess her adrenal function at this time. The most recent assay may be slightly elevated but at least one menstrual period has occurred without cortisone therapy.

In 1951 Wilkins and co-workers[2] suggested that perhaps long-continued treatment might render the adrenals permanently incapable of their former hyperactivity. There is evidence that short-term cortisone therapy certainly does not prevent the return of the adrenal hyperactivity.[20] There have been no specific studies that indicate what long-term therapy might accomplish in this regard. In at least one, and perhaps both, of our patients such sustained suppression of adrenal androgenic hyperactivity may have occurred.

At birth the infants of both patients were normal by all the usual standards. Fears have been expressed that treatment of pregnant patients might be followed by adrenal insufficiency in the infants in the neonatal period. Neither infant showed such effects nor has there been mention of this difficulty in similar instances in the literature. It appears, therefore, that this possibility need be of little concern.

References

1. Wilkins, L., Lewis, R. A., Klein, R., and Rosemberg, E.: Bull. Johns Hopkins Hosp. **86**: 249, 1950.
2. Wilkins, Lawson, Lewis, R. A., Klein, Robert, Gardner, L. I., Crigler, J. F., Jr., Rosemberg, Eugenia, and Migeon, C. J.: J. Clin. Endocrinol. **11**: 1, 1951.
3. Bartter, F. C., Albright, Fuller, Forbes, Anne P., Leaf, Alexander, Dempsey, Eleanor, and Carroll, Evelyn: J. Clin. Invest. **30**: 237, 1951.
4. Yamashita, T., and Kozakae, F.: Endocrinologia japonica **3**: 176, 1956.
5. Ingle, D. J., and Kendall, E. C.: Science **86**: 245, 1937.
6. Ingle, D. J.: Am. J. Physiol. **124**: 369, 1938.
7. Ingle, D. J., and Mason, H. L.: Proc. Soc. Exper. Biol. & Med. **39**: 154, 1938.
8. Sprague, R. G., Power, M. H., Mason, H. L., Albert, A., Mathieson, D. R., Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Arch. Int. Med. **85**: 199, 1950.

9. Sprague, R. G., Mason, H. L., and Power, M. H.: In Pincus, Gregory, editor: Recent Progress in Hormone Research, New York, 1951, Academic Press, Inc., vol. 6, pp. 315-372.
10. Wilkins, Lawson, Gardner, L. I., Crigler, J. F., Jr., Silverman, S. H., and Migeon, C. J.: J. Clin. Endocrinol. **12**: 257, 1952.
11. Wilkins, Lawson, Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J.: J. Clin. Endocrinol. **12**: 1015, 1952.
12. Wilkins, Lawson, Crigler, J. F., Jr., Silverman, S. H., Gardner, L. I., and Migeon, C. J.: J. Clin. Endocrinol. **12**: 277, 1952.
13. Bongiovanni, A. M., Eberlein, W. R., and Cara, José: J. Clin. Endocrinol. **14**: 409, 1954.
14. Jones, H. W., Jr., and Jones, G. E. S.: Am. J. Obst. & Gynec. **68**: 1330, 1954.
15. Jones, G. E. S., Howard, J. E., and Langford, H.: Fertil. & Steril. **4**: 49, 1953.
16. Greenblatt, R. B.: Am. J. Obst. & Gynec. **66**: 700, 1953.
17. Greenblatt, R. B., Barfield, W. E., and Lampros, C. P.: Fertil. & Steril. **7**: 203, 1956.
18. de Alvarez, R. R., and Smith, E. K.: Obst. & Gynec. **9**: 426, 1957.
19. Wilhelm, S. F., and Marks, R. G.: J. Urol. **73**: 17, 1955.
20. Goldberg, Minnie B.: J. Clin. Endocrinol. **14**: 389, 1954.

Discussion

DR. E. STEWART TAYLOR, Denver, Colo.—These 2 cases illustrate one of the forms of the adrenogenital syndrome. This, of course, is dependent on the time of development as well as the sex of the individual affected. The condition is about five times as common in the female as in the male.

Children with congenital adrenal hyperplasia show excessive masculinization, increased protein anabolism, rapid somatic growth, and accelerated epiphyseal ossification, in addition to characteristic laboratory findings. When the syndrome develops in the postnatal period before puberty, it is usually secondary to a functioning adrenal tumor, but it may be from acquired adrenal cortical hyperplasia. Seborrhea, acne, and development of sexual hair may be the first signs. These are followed by hypertrophy of the clitoris, deepening of the voice, rapid growth, and epiphyseal development. When the condition develops near or after puberty, it may be secondary to either tumor or hyperplasia.

Hirsutism (masculine in type), hypertrophy of the clitoris, deep voice, and excessive musculature suggest the condition. Although all patients with the syndrome show virilization and increased protein anabolism because of excessive secretion of androgens, there are differences in the other functions of the adrenal cortex. Briefly, one fourth show a tendency to sodium loss and elevated serum potassium with resultant dehydration, circulatory collapse, and even cardiac arrest from hyperkalemia. Some may have hypertension, possibly from sodium retention. There may be a tendency to hypoglycemia in some patients caused by a deficit of glycogenic hormone.

We would classify these 2 cases as androgenital syndrome with postnatal virilization instead of congenital androgenitalism. Whether the condition is congenital or acquired, the basic abnormality appears to be an enzymatic defect in the adrenal cortex preventing the synthesis of compound F and the subsequent formation of abnormal amounts of metabolites from Δ^5 pregnenolone, progesterone, and 17-hydroxyprogesterone. The pathology consists of enlargement of the adrenals primarily because of hyperplasia of the reticular zone. The fascicular zone is disorganized and is infiltrated with cells from the reticular zone. The glomerular zone may be absent.

The condition occurs frequently in siblings born from apparently normal parents. Childs and Grumbach suggest that the disorder may be a manifestation of a recessive trait which may express itself only in a homozygous offspring. Theoretically, the mutant gene may occur about once in 125 individuals.

We currently are following 2 sisters at the Colorado General Hospital who in most respects are similar to the first patient reported by Dr. Wilson. The older sister was treated with cortisone in 1955. Menses ensued one month later and she soon became pregnant. The patient began labor spontaneously at term and after a short trial was delivered by cesarean section because of a contracted, android-type pelvis. Her 2,520 gram daughter was normal

in all respects. It is interesting to note that the only vaginal bleeding this patient had ever had before cortisone therapy was after the administration of estrogen by her private physician. The patient continued to menstruate normally for eight months following delivery, without steroid therapy, when she had an episode of menorrhagia which was successfully treated by uterine curettage. The younger sister was also treated with cortisone. Prompt menses occurred, she has since married, and is now in her second month of pregnancy. It was interesting to us that the first response to cortisone therapy in each of these patients was enlarging, painful breasts which occurred about 2 weeks after treatment started. Both of the patients had little or no noticeable breast tissue before cortisone treatment.

Dr. Dalton Jenkins, our endocrinologist, has a patient, a third patient, who falls in the category of the 2 reported by Dr. Wilson, and the 2 patients discussed from our clinic. Two of the 3 patients from the Colorado General Hospital have shown increasing excretions of pregnanetriol while excreting normal amounts of 17-ketosteroids. It is Dr. Jenkins' feeling that, in the early phases of this syndrome, pathological levels of excreted pregnanetriol may antedate the appearance of abnormal levels of 17-ketosteroids in the urine.

Obstetrics

THE LIVING HUMAN OVUM*

LANDRUM B. SHETTLES, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women)

THIS presentation concerns cytological aspects of the living human ovum, its source of nourishment, and very early stages in its development. The intricacies of the female germ cell are clearly illustrated.

Material and Method

Ova were obtained by either aspiration of follicles with a syringe and needle or irrigation of the Fallopian tube with physiological saline and a pipette attached to a rubber bulb in patients in whom there was evidence of recent ovulation. The ovum was observed and photography by means of phase contrast microscopy.

Observations

The ovum upon ovulation is surrounded by some 3,000 to 4,000 corona radiata cells (Fig. 1). If the ovum is kept at 37° C. for 3 hours in the presence of bits of Fallopian tubal mucosa in physiological saline or follicular fluid and then gently aspirated and expressed with a fine pipette, it may be released with the zona pellucida completely denuded of cells (Fig. 2). As may be noted at ovulation, the first polar body is already formed; the ovum is ready for fertilization. There is marked homogeneity in the ooplasm. The cytoplasmic membrane is represented by the limiting boundary of the ooplasm. The ovum with the zona pellucida removed remains intact. The perivitelline space into which the first polar body is released is filled with a granular liquid suspension. The mature ovum measures from 100 to 150 microns in diameter, to the outer surface of the zona pellucida.[1] The zona pellucida possesses great elasticity. Ova vary not only in size but in shape. The ovum and the polar body are of yellow color. The intensity of the yellow color varies from specimen to specimen. Early division of the first polar body may be noted in Fig. 2.

*Presented at a meeting of the New York Obstetrical Society, Nov. 12, 1957.

After enzymatic action of the tubal mucosa, the ovum may be so aspirated and expressed with the pipette as not to dislodge all of the corona radiata cells (Fig. 3). The corona radiata cells vary in size and shape (Figs. 3-11). As illustrated, the corona radiata cells near the zona pellucida have cannules or tubular processes which extend through the zona pellucida to its inner surface.

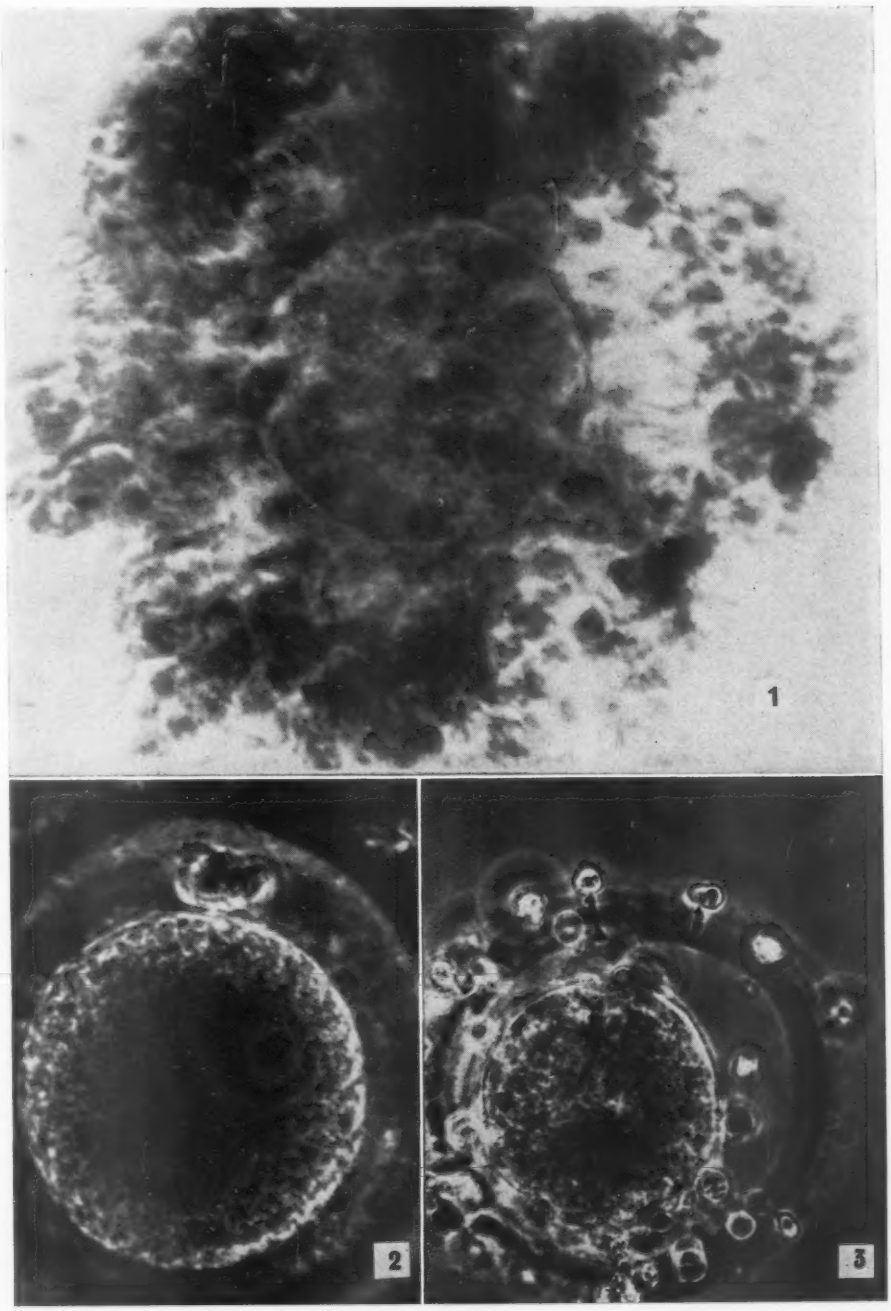

Fig. 1.—Very fresh tubal ovum. (×100; reduced ½.)

Fig. 2.—Ovum shown in Fig. 1 after complete denudation of corona radiata cells. (×200; reduced ½.)

Fig. 3.—Partially denuded ovum showing tubules of corona radiata cells extending through zona pellucida. (×100; reduced ½.)

The truly granular nature of the corona radiata cell is shown in Fig. 4. The refractive index of the granular material within the cell, its tubular extension through the zona pellucida and the perivitelline space are the same. The granules can be observed in their passage from the cell proper along its cannule into the space about the egg (Figs. 8 and 11). Cilia surround the inner ostia of some of the cellular tubules. The beating of these cilia mixes the granules in the suspension, i.e., the ovum is bathed in granules. The corona radiata cells not in closest proximity to the zona pellucida are connected with one another through their intercellular tubular processes (Fig. 5). When the corona radiata cell is filled with the granular material, its nucleus may be very clearly seen (Fig. 7). After the material is released through the tubular extension into the perivitelline space, the remaining nucleus practically fills the cell, i.e., almost all of the granular cytoplasm is discharged into the space about the ovum (Fig. 8).

It is during the passage of the ovum along the Fallopian tube that the zona pellucida becomes completely freed of the corona radiata cells. This occurs whether the egg is fertilized or not. The exact time required is not known.[2]

Often somewhat eccentric within the cytoplasm is the nucleus of the ovum in which there is a single nucleolus (Fig. 12). The nucleus is round and possesses a uniformly thin nuclear membrane. The nucleolus may be dissected free as shown in Fig. 13; it is often eccentric within the nucleus.

Preparatory to release of the first polar body, the nucleus of the ovum migrates to just beneath the cytoplasmic membrane (Fig. 14). The first polar body, almost formed, between the ovum and the zona pellucida is seen in Fig. 16. The completely denuded ovum in Fig. 15, with the first polar body formed but still in close proximity to the egg, shows spermatozoa penetrating the zona pellucida. The first polar body is completely free in the perivitelline space in Fig. 17. The polar bodies vary in size and shape. Division of the first polar body may occur before the second one is released (Fig. 18). In Fig. 19 the first polar body has divided and the second one is formed. Like the remaining ovum, each of the 3 polar bodies contains the haploid number of chromosomes and is capable of being fertilized.

Spermatozoa come in contact with the egg by chance; they may swim in the closest proximity to the zona pellucida and yet show no trophic influence. Having once accidentally touched the ovum, the spermatozoa become oriented at right angles to the surface of the zona pellucida and almost invariably remain in contact with it (Fig. 23). Through the marked, synchronized beating of the spermatozoan tails the ovum is often rotated clockwise for many hours as rapidly as 360 degrees in 15 seconds. The ovum is often moved about within the medium and simultaneously rotated.

The entire spermatozoon penetrates the ovum (Fig. 24). More than one may pass into the ooplasm. The movement of the spermatozoan tail within the ooplasm brings the head into close proximity with the egg nucleus.

Cleavage of the ovum occurs after exposure to spermatozoa in vitro at 37° C. In Fig. 22 is a 2 cell stage developed after 29 hours, and in Figs. 20 and 21 are two views of a morula stage developed after 72 hours.[3]

Comment

The disposition of the hundreds of corona radiata cells over the entire surface of the zona pellucida is considered indicative of their role in the growth and maturation of the ovum. The extension from each corona radiata cell through the zona pellucida enables a granular liquid to be emptied into the

perivitelline space surrounding the egg. This is believed to be a nutritive material for the ovum within the follicle and during the first part of its sojourn within the Fallopian tube.

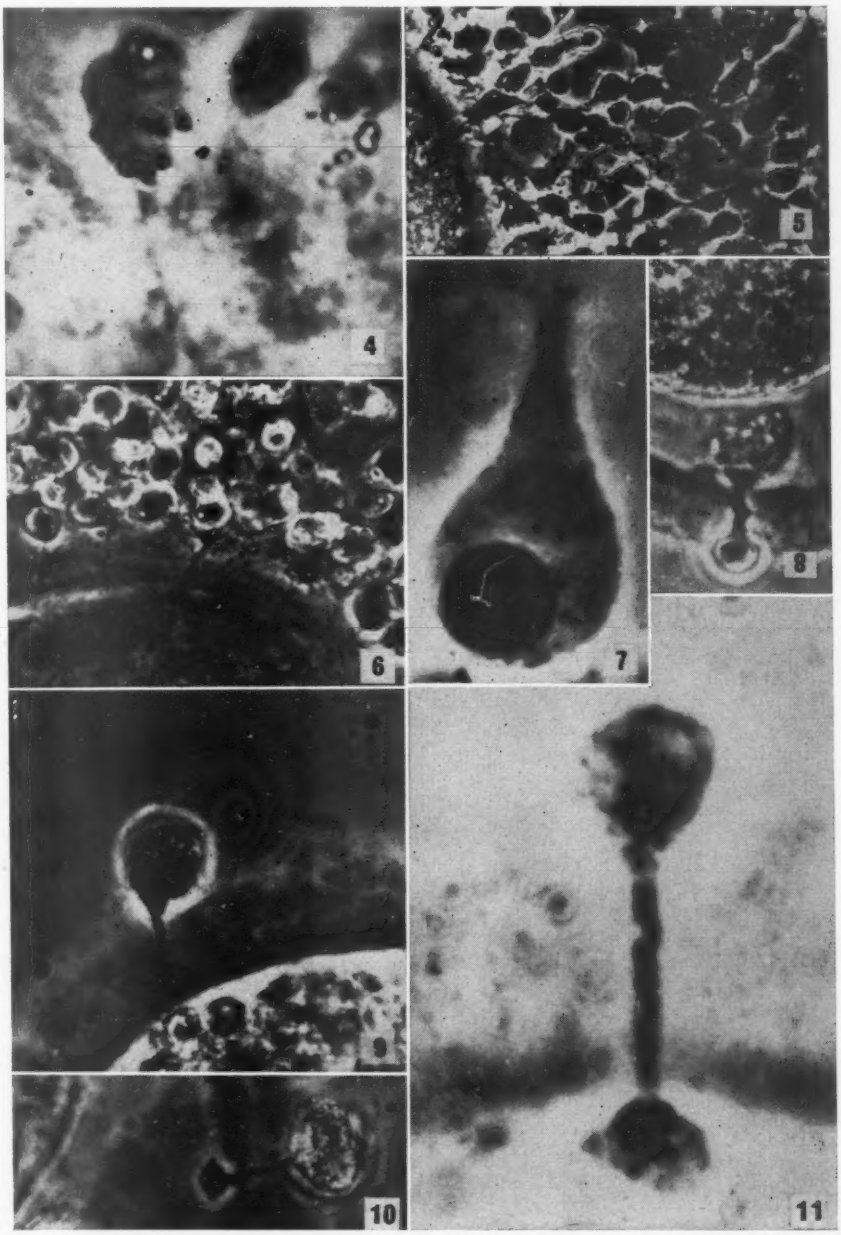

Fig. 4.—Granules in corona radiata cell. (×800; reduced ½.)
Fig. 5.—Corona radiata cells connected through extensions. (×800; reduced ½.)
Fig. 6.—Extensions of corona radiata cells through zona pellucida. (×800; reduced ½.)
Fig. 7.—Filled corona radiata cell with prominent nucleus (×1,200; reduced ½.)
Fig. 8.—Corona radiata cell after complete release of granular cytoplasmic contents into the perivitelline space. (×1,000; reduced ½.)
Fig. 9.—Corona radiata cell with cannule. (×800; reduced ½.)
Fig. 10.—Corona radiata cell with cannule. (×800; reduced ½.)
Fig. 11.—Granules in corona radiata cell and its extension. (×1,200; reduced ½.)

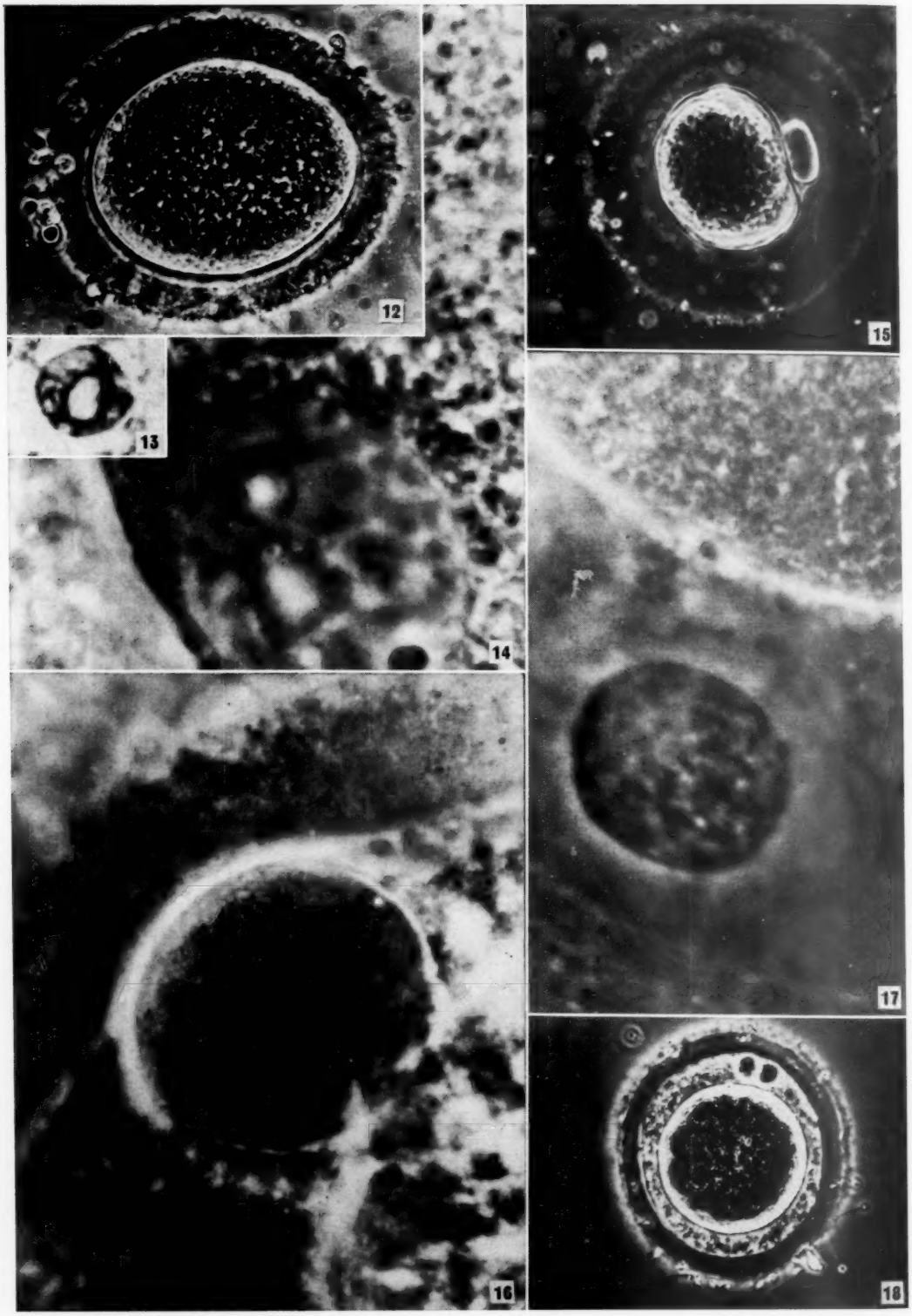

Fig. 12.—Ovum with eccentric nucleus and nucleolus. (×100; reduced 3/5.)

Fig. 13.—Structure of nucleolus dissected free. (×1,200; reduced 3/5.)

Fig. 14.—Nucleus having migrated to just beneath cytoplasmic membrane preparatory to release of first polar body. (×400; reduced 3/5.) (From Shettles.[1])

Fig. 15.—First polar body formed; spermatozoa in zona pellucida (×100; reduced 3/5.) (From Shettles.[1])

Fig. 16.—First polar body almost formed. (×400; reduced 3/5.) (From Shettles.[1])

Fig. 17.—First polar body free in perivitelline space. (×400; reduced 3/5.)

Fig. 18.—Dividing first polar body (×100; reduced 3/5.) (From Shettles.[2])

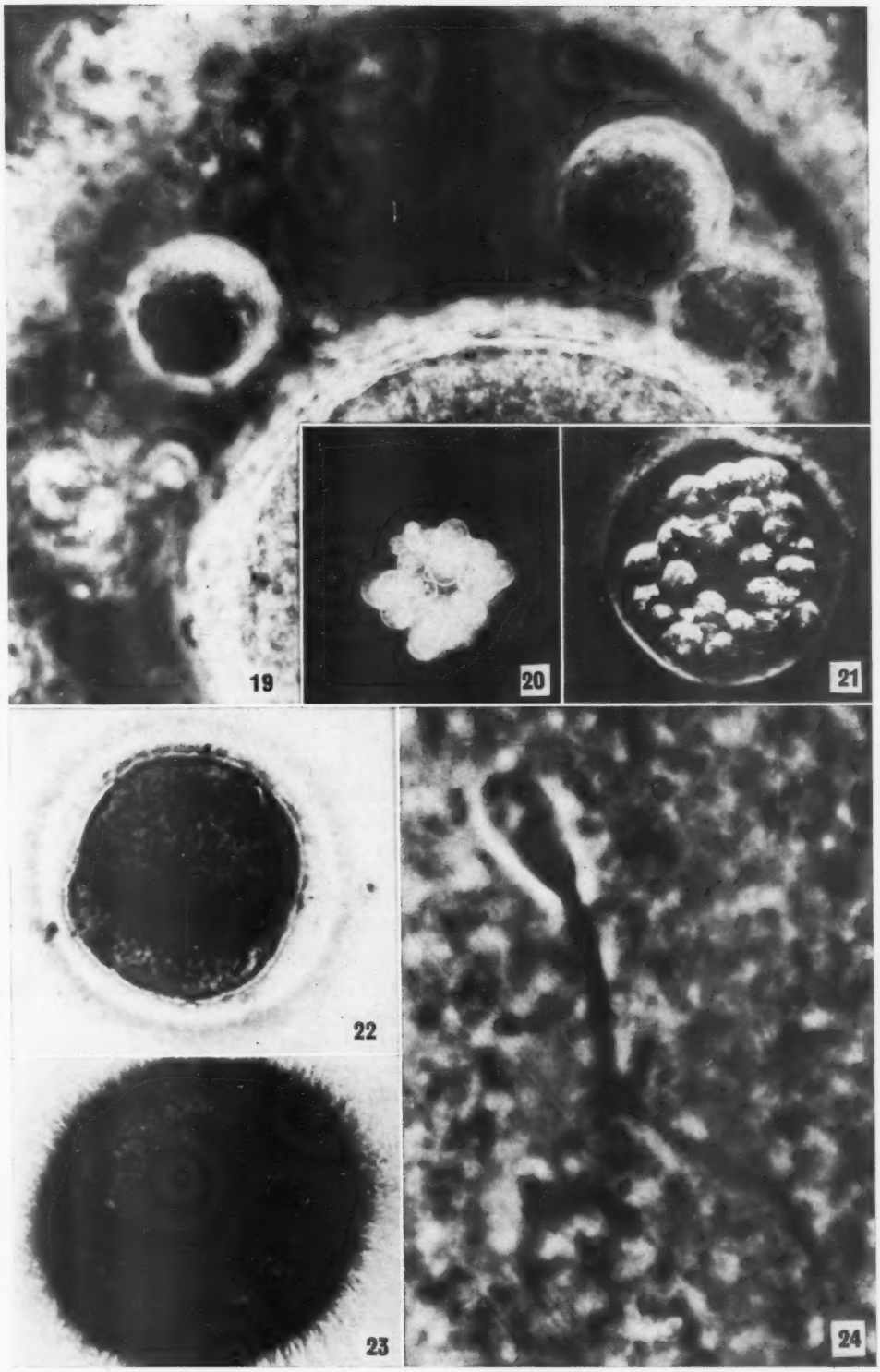

Fig. 19.—Ovum containing 3 polar bodies, the first having divided. (×400; reduced ½.)
Fig. 20.—Morula stage. (×100; reduced ½.) (From Shettles: Fertil. & Steril. 6: 287, 1955.)
Fig. 21.—Another view of morula stage in Fig. 20. (×100; reduced ½.) (From Shettles: Fertil. & Steril. 6: 287, 1955.)
Fig. 22.—Two-cell stage. (×100; reduced ½.)
Fig. 23.—Innumerable spermatozoa with heads against zona pellucida. (×100; reduced ½.)
Fig. 24.—Entire spermatozoon within ooplasm. (×1,000; reduced ½.) (From Shettles.[1])

It appears that when the pressure within the corona radiata cell exceeds the constricting effect of the zona pellucida about the tubular extension, then its granular contents are expelled into the perivitelline space.

Within the Fallopian tube, the surface of the zona pellucida in time becomes completely free of the corona cells. This denudation of the zona pellucida makes for more ready passage of the ovum. When it is fertilized in the outer one third of the tube, the great elasticity of the denuded zona pellucida undoubtedly helps in maintaining the integrity of the ovum during the early stages of cleaving and expanding which occur during its passage through the tube into the uterine cavity. The zona pellucida is still intact when the dividing ovum reaches the uterine cavity. It is considered possible that tubal implantation might result should premature release of the fertilized ovum occur through rupture of the zona pellucida.

In that the two polar bodies resulting from division of the first one and the second polar body have the haploid chromosomal constituency like the remaining ovum, nothing is seen to prevent multiple pregnancy resulting from fertilization of one or more polar bodies in addition to the ovum. Penetration of more than one spermatozoon through the zona pellucida into the perivitelline space favors this possibility. Accordingly, certain types of twin pregnancy may be explained.

The yellow color of the ooplasm and polar body cytoplasm is in keeping with their containing yolk. The amount and distribution of yolk indicated by the yellow color would be typical for an isolecithal ovum.

Summary

Living human follicular and tubal ova have been studied by means of phase contrast microscopy, with special reference to the cytology and physiology of the corona radiata cells, polar body formation, cytoplasmic and nuclear constituents, spermatozoan behavior about and penetration of the ovum, and early cleavage. The ooplasm and polar body cytoplasm have been found to be yellow in color.

References

1. Shettles, L. B.: Am. J. Obst. & Gynec. **66**: 235, 1953.
2. Shettles, L. B.: Am. J. Obst. & Gynec. **69**: 365, 1955.
3. Shettles, L. B.: Fertil. & Steril. **6**: 287, 1955.

Discussion

DR. EARL ENGLE, New York, N. Y.—Among the most dramatic productions of Dr. Shettles' laboratory are these pictures of the cells of the corona radiata and the granulosa cells, which are transmitting into the cytoplasm of the egg cells seriated globules of substance, presumably other bits of protoplasm. These really represent a new concept in the biology of the egg cell. I am not aware that this phenomenon has been reported by those studying other mammalian ova. I am intrigued with the observations. These are viable cells. A moving film of intracellular projection might serve to inform us all and dispel whatever doubts we might have. Dr. Shettles has this in mind.

We have been taught that the human trophoblast by a process described as pinocytosis is capable of sending out protoplasmic projections and engulfing bits of serum protein and

imbibing it. It is really not biologically absurd to think that these cells of the corona radiata may be actually and practically transmitting to the cytoplasm of the egg needed metabolites. Dr. Shettles did not say so, but his report would have us believe that the cells of the granulosa act as a set of steri-jets or spongules to supply needed metabolic agents.

At the present these observations cannot be properly evaluated. I am impressed with the technical facility of the photography and the observations which it entails. I do not know the meaning. I do not know whether these are completely viable cells, both the corona radiata and granulosa cells and the recipient egg. But, as Dr. Shettles knows, research is always slow, and all new ideas and new concepts will inevitably be met with skepticism until further work and further observations show us indubitably that we are dealing with a vital biological process.

DR. JOHN ROCK, Boston, Mass.—I wonder whether the men who are so closely associated geographically, if not scholastically, with a man like Shettles realize what a contribution he has made. As far as I am aware (of course we have not heard from Russia lately), he is the only man in the world who could show you what he has shown you and tell you what he has told you of the very first stages of human conception.

There are various details about the effect of the tubal environment on the ovum that I wish I had time to bring out. Does the oviduct make any significant contribution to spermatozoa? Dr. Shettles rather suggests in his paper that the spermatozoon may be perfectly good morphologically when delivered to the cervix, but it is not any good to the ovum until after it has passed through the tube and been conditioned by the latter. He has added tubal epithelium to his culture medium and has been more successful than anybody else who has attempted in vitro fertilization.

The clinical significance of Dr. Shettles' work should not be lost upon us. He has shown us what the egg looks like. He has shown the time interval that is necessary before a follicular egg in vitro divides into a multiblastomere stage, similar to what Dr. Hertig has shown of eggs in vivo. We must remember that in nearly all mammals with which we are familiar, regardless of the length of the tube, the ovum reaches the uterus about the fourth day after fertilization; and fertilization takes places within about 12 hours of ovulation. The human egg probably is not susceptible to fertilization for much longer than 12 hours. These details I think are of great clinical value.

Dr. Shettles has not yet told us that he is ready to apply his in vitro fertilization toward impregnating women. This may be because he has been devoting so much time to the egg he has not realized that with the new steroids now available it is possible in about 4 days of treatment to change the endometrium from an early proliferative stage to the condition found 4 days after ovulation. The time may be rapidly approaching when the poor woman whose tubes have been excised, yet who still wants a baby, will rejoice that Dr. Shettles will be able to extract an ovum from her ovary, probably not by laparotomy, but through an operating telescope (which can be done—we have done it); then fertilize the egg in vitro by the husband's spermatozoa; and finally put it back in the uterus. Thus will he impregnate the woman in spite of the fact that she has no tubes.

I am not sure that I follow him exactly on his hypothesis about ectopic pregnancy. This breaking out of the vitellus by premature rupture of the zona pellucida leaves me a little cold because one still has to have the trophoblast and the differentiation of cells which we have shown here to make it possible for the egg to take advantage of the maternal blood supply.

DR. SHETTLES (Closing).—With respect to Dr. Rock's remarks about ectopic pregnancy, it seemed to me that, should the zona pellucida for some reason break, as the ovum passes down the tube, after fertilization, the cleaving and expanding cellular mass might become attached to the tubal mucosa and lead to an ectopic pregnancy. It is speculation. I do not see how it can ever be proved. We do know, however, whether the ovum is fertilized or not, the corona radiata cells become completely cleared away during the passage of the egg

down the tube. This is from the enzymatic action of the tubal mucosa possibly aided by tubal peristalsis. Consequently, the ovum becomes very smooth and undoubtedly is more easily passed on into the uterus. We know from specimens observed by Drs. Rock and Hertig that normally the zona pellucida is intact around the dividing egg upon entry into the uterine cavity.

The zona pellucida may also be looked upon as the container for the nutritive bath in which the ovum matures in situ in the ovary, and during its transit through the Fallopian tube in the event of fertilization.

A-B-O(H) BLOOD GROUP SUBSTANCES IN THE HUMAN MATERNAL-FETAL BARRIER AND AMNIOTIC FLUID*

VINCENT J. FREDA, M.D., NEW YORK, N. Y.

(From the Department of Obstetrics and Gynecology, College of Physicians and Surgeons, Columbia University, and the Sloane Hospital for Women, Columbia-Presbyterian Medical Center)

THE finding of fetal blood group substances in the placental tissue is neither surprising nor new. Fetal blood group substance has been found in maternal tissue in two instances[2] but the significance of this finding has never been determined. The occurrence of maternal blood group substance in fetal tissue or amniotic fluid has never been reported. In 1928 von Oettingen and Witebsky[1] reported finding the presence of group A substance in the placenta in a case in which the infant was group A. In 1932, Reich[2] and Witebsky and Reich[3] studied the placental tissue for the presence of group A substance and correlated their findings with the blood groups of the mother and infant. They found that when the mother was group A, the decidua vera always contained A substance and that the decidua basalis always had less A substance than the decidua vera. They also reported that when the fetus was group A, the amnion always had the A substance and the placental villi never contained it. They drew attention to two unique cases; in the first of these, A substance was found in the decidua vera when the mother was group O and the fetus group A; in the second case A substance was found in the decidua vera when the mother was group B and the fetus group A. They indicated surprise at finding fetal group substance in maternal tissue and stated that this finding merited further investigation. As will be pointed out later in this paper, this observation was probably related to the secretor status of the infant.

This study was initiated in an attempt to localize the blood group substances A, B, and O(H) in the amniotic fluid and in the various tissues interposed between mother and fetus, and to relate this information to their respective blood groups and secretor statuses. It is hoped that such a study may eventually shed some light on the mechanism of A-B-O hemolytic disease and provide further insight into the exchange of large molecular weight substances between mother and fetus.

As referred to in this paper, the maternal-fetal barrier includes all of the following: amnion, membranous chorion (chorion laeve), decidua vera, villous placenta, and that portion of the decidua basalis which is expelled with the

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placenta. The term "fetal membranes" denotes the amnion and membranous chorion; it does not include the chorionic plate and placental villi although anatomically and physiologically the villi comprise a membrane of fetal origin.

The blood group substances A and B are not restricted to the red blood cells but also occur in most of the body cells.[6] Approximately 80 per cent of the population have the blood group substances present in their tissue secretions as well and these individuals are called secretors.[5] Those who do not have the blood group substance present in their secretions are called nonsecretors. Apparently, there are some individuals who are "weak" secretors (viz., saliva inhibition titers of 1:4 or less) and in this paper these individuals are arbitrarily classified as nonsecretors. Whether or not a person is a secretor seems to be determined by a pair of Mendelian genes.[7] All secretors, regardless of blood group, secrete an "H" substance[7, 11]; thus the tissue secretions from any secretor, irrespective of blood group, are capable of neutralizing anti-H. Although "H" has been shown to be immunologically different from "O," anti-H will agglutinate group O red cells (it will also agglutinate A_2 red cells and to a lesser extent A_1 and B red cells).

The more commonly known sources for anti-H are certain plant seeds and absorbed animal sera.[8, 9, 10] For this study anti-H extracted from *Ulex europaeus* seeds was used to identify the secretor status of group O individuals and to determine the presence of O(H) substance (i.e., O and/or H substance) in all the fluids and tissue solutions studied. When either mother or fetus or both are secretors, regardless of blood group, they are capable of contributing H substance to the tissues of the M-F barrier and amniotic fluid.

Materials and Methods

The material for this study was obtained from 20 normal full-term deliveries at the Sloane Hospital for Women.

The various fluids and tissues that were studied are as follows: maternal and fetal saliva, amniotic fluid, amnion, membranous chorion with adherent decidua vera, and the placenta proper. In 5 of the 20 cases the maternal and fetal sera were also studied, and in these same 5 cases the decidua vera, membranous chorion, decidua basalis, and villous placenta were each studied as separate tissues.

The amniotic fluid was obtained during labor under sterile conditions, by puncturing the intact sac via the cervical os with a spinal needle and drawing off into a syringe approximately 5 c.c. of amniotic fluid. If the fluid was blood tinged or meconium stained, the case was not included in the study. After delivery of the placenta and membranes, 3 to 5 c.c. of cord blood was obtained and the placenta was rinsed with saline to remove blood and adherent serum. The amnion was stripped from the chorionic membrane and decidua vera and a portion of each was taken for study. A full-thickness section (excluding the amnion) of the placenta was obtained. In 5 cases the chorionic membrane was stripped from the decidua vera and the decidua basalis was separated from the villous portion of the placenta and all four tissues were studied separately. The infant's saliva was collected after the stomach had been aspirated and the nasopharynx had been thoroughly cleared of mucus and amniotic fluid. All specimens of saliva were momentarily heated over the open flame of the Bunsen burner in order to destroy the heat-labile enzyme which inactivates blood group substance.[12]

A pilot study utilizing two different methods of extraction was carried out in 2 cases in order to compare the amount of blood group substance recovered, as estimated by the agglutination inhibition method. A saline extraction method, described below, was compared with an ethanol precipitation method.[15] Since it proved to be the simpler method and since there was no significant difference in the amount of group substance recovered, the saline extraction method was used. For the saline extraction method each specimen of tissue was blotted to remove surface moisture and a 5 Gm. sample was homogenized with 10 c.c. of isotonic saline in the semi-micro Monel metal container of the Waring Blendor. The suspension was then centrifuged and the supernatant was decanted and tested.

The presence of A, B, and O(H) substances was determined by the hemagglutination inhibition method. A 1:10 dilution with saline of commercial preparation of human A and B agglutinin* and a 1:5 dilution of anti-H (Ulex) were used. Fresh 2 per cent red-cell suspensions of groups A, B, and O were used to demonstrate the agglutination inhibition. It was felt that more sensitivity could be obtained by allowing reactions to take place in the open wells of the agglutination slide. All reactions were allowed to take place over a 20 minute period in an incubator set at 37° C. When working with anti-H (Ulex) the recommendations outlined by Wiener[12] were used. To screen for the presence of group substance, 2 drops of each unknown were allowed to react with 1 drop each of anti-A, anti-B, and anti-H for a 20 minute period. Following this, 1 drop of a 2 per cent red-cell suspension (A, B, and O) was added and after 20 minutes in the incubator the results were read microscopically. For reactions with anti-H (Ulex), the refrigeration technique was employed. If group substance was found in a particular solution, titration was carried out. In order to demonstrate a higher titer with a definite end point, 2 drops of each dilution were allowed to react with 1 drop of antisera (constant concentration) in the well of the slide.

All reactions were read microscopically and graded from negative to 4 plus. Four-plus clumping was very obvious to the naked eye; 1 plus represented an occasional small clump of red cells on microscopic examination; "trace" represented doubtful evidence of clumping microscopically; "negative" was no evidence of clumping under the microscope. In reporting the results, only negative and trace reactions were recognized as showing inhibition and anything more than a trace was considered as lacking inhibition. The titers as expressed in this paper represent the last dilution at which no clumping was observed. In each case the solutions were examined not later than 18 hours after collection, and in the majority of cases they were tested immediately after collection. When not in use, all specimens and solutions were kept in the refrigerator at plus 4° C. All the inhibition tests were carried out by one person, and in 10 of the 20 cases the tests were repeated by a second person with virtually identical results.

In 5 cases in which either the maternal antigen was found in the amniotic fluid or the fetal antigen in the decidua vera, these titers were compared with the inhibition titers in the respective maternal and fetal sera.

In this paper when denoting the blood group of both mother and infant, the mother's group will be placed over the infant's group (i.e., if the mother is group A and the fetus is group O, this will be expressed as A/O). The numerator refers to the mother and the denominator denotes the fetus. For the sake of consistency in recording, the word "fetal" is sometimes used where "infant" or "newborn" would more properly be the terminology.

*Anti-A and anti-B blood grouping serum (human), supplied by The Department of Health, City of New York.

In every case all materials to be tested were first screened for the presence of specific blood group substance and, if it was found, titrations were carried out and recorded as shown in Table I. Each solution was tested for specific agglutinins against A, B, and O red cells before the inhibition tests were run. The inhibition tests were carried out for all three group substances in each case, to verify the group specificity of the reaction. Where negative results are indicated, it does not necessarily follow that a small amount of group substance could not be present. It simply means that by the methods used in this study none was found. All figures are presented primarily for the purpose of comparing one case with another and one tissue with another.

TABLE I. CASE METHOD FOR RECORDING THE PRESENCE OF BLOOD GROUP SUBSTANCE

CASE NO. 834980 MOTHER—GROUP B FETUS—GROUP O	A	B*	O(H)*
Maternal serum	Neg.	Neg.	Neg.
Fetal serum	Neg.	Neg.	Neg.
Maternal saliva	Neg.	32/64	—
Fetal saliva	Neg.	Neg.	16/128
Amniotic fluid	Neg.	2/64	4/128
Amniotic membrane	Neg.	Tr./64	Tr./128
Chorionic membrane	Neg.	Tr./64	Tr./128
Decidua vera	Neg.	1/64	1/128
Decidua basalis	Neg.	Neg.	Tr./128
Villous placenta	Neg.	Neg.	Tr./128

*The numerator indicates the inhibition titer of the substance tested, and the denominator indicates the titer of the control substance.†

†Control for A and O(H), Blood Group Specific Substances A and B (Merck Sharp and Dohme). Control for B, Human B Saliva. This method of reporting the results was suggested by Dr. A. S. Wiener.

Results

The results are recorded in Tables II and III. Table III includes maternal and fetal sera, chorionic membranes, and decidua basalis, in addition to the substances studied in Table II. The amount of group substance found in the amniotic fluid and tissue solutions was small when compared to the reference standards. Even where the titer was only one unit, however, this represented a group-specific reaction showing complete inhibition and one that could be repeated with the same results. It is apparent, from Tables II and III, that, when the mother was a secretor, her blood group substance was found in the amniotic fluid and a trace of the antigen could be found in the amnion, chorionic membrane, and decidua vera. Likewise, when the fetus was a secretor, the fetal antigen was almost always found in the decidua vera as well as in the amniotic fluid and membranes. Also when the fetus was a secretor, its antigen was at least 4 to 16 times as concentrated in the amniotic fluid as when the fetus was a nonsecretor. When the mother was a nonsecretor, her blood group substance was not detected in fetal tissue and likewise, when the fetus was a nonsecretor, its antigen was not found in maternal tissue. Occasionally, blood group substance was detected in the placental villi.

TABLE II. BLOOD GROUP AND SECRETOR STATUS OF MOTHER AND FETUS AND THE A-B-O(H) ANTIGENS IN THE TISSUES AND AMNIOTIC FLUID OF THE M-F BARRIER

UNIT NO.	BLOOD GROUP MATERNAL/ FETAL	SECRETOR STATUS*	AMNIOTIC FLUID	AMNION	DECIDUA VERA AND CHORIONIC MEMBRANES	PLACENTA PROPER	CONTROL† A	CONTROL† B	CONTROL† O(H)‡
2622842	A/A	NS/NS	A-tr.	A-tr.	A-tr.	A-tr.	64		
303388	A/A	S/S	A-32	A-8	A-8	A-tr.	64		
294365	B/B	S/NS	B-8	B-tr.	B-2	B-tr.		64	
293043	O/A	S/S	O-4 A-2	O-2 A-2	O-4 A-tr.	O-tr. A-neg.	64		128
222392	B/B	NS/NS	B-tr.	B-tr.	B-tr.	B-tr.		64	
247857	A/O	S/S	A-2 O-8	A-tr. O-4	A-tr. O-tr.	A-neg. O-neg.	64		128
1322680	A/A	NS/S	A-16	A-4	A-2	A-1	64		
171806	A/A	S/S	A-8	A-1	A-1	A-neg.	64		128
295845	O/O	S/S	O-4	O-1	O-tr.	O-neg.			
707722	A/AB	NS/NS	Neg.	Neg.	Neg.	Neg.	64	64	
303357	A/O	S/S	A-4 O-16	A-tr. O-1	A-tr. O-tr.	A-neg. O-neg.	64		128
227529	A/O	S/S	A-2 O-16	A-tr. O-1	A-1 O-tr.	A-neg. O-neg.	128		256
301075	O/O	NS/NS	Neg.	Neg.	Neg.	Neg.			256
980510	A/O	NS/S	A-neg. O-4	A-neg. O-1	A-neg. O-tr.	A-neg. O-tr.	128		256
130320	O/O	S/NS	O-tr	O-neg.	O-neg.	O-neg.			128
690570	A/O	S/S	A-1 O-8	A-tr. O-tr.	A-tr. O-tr.	A-neg. O-neg.	64		128
303387	O/A	NS/NS	O-neg. A-tr.	O-neg. A-tr.	O-neg. A-neg.	O-neg. A-neg.	64		128

*S, Secretor. NS, Nonsecretor.

†Control, Blood Group Specific Substances A and B (Merck Sharp & Dohme) was used as standard reference for A and H. Human B saliva was used as standard reference for B. All numerical figures from 1 to 256 represent inhibition titer (the last dilution of the substance at which no clumping was observed).

‡O actually represents O plus H substance.

As shown in Table III, in the cases of maternal-fetal heterospecificity when the mother was a secretor, the maternal antigen was more concentrated in the

TABLE III. BLOOD GROUP AND SECRETOR STATUS OF MOTHER AND FETUS AND THE A-B-O(H) ANTIGEN IN THE M-F BARRIER AND AMNIOTIC FLUID

UNIT NO.	BLOOD GROUP MATERNAL/FETAL	SECRETOR STATUS*	MATERNAL SERUM	FETAL SERUM	AMNIOTIC FLUID	AMNIOTIC MEMBRANE	CHORIONIC MEMBRANES	DECIDUA VERA	DECIDUA BASALIS	VILLOUS PLACENTA	CONTROL† A	CONTROL† B	CONTROL† O(H)
303358	A / O	S / S	Neg.	Neg.	A-1 O(H)-8	A-neg. O(H)-1	A-neg. O(H)-1	A-neg. O(H)-1	A-neg. O(H)-1	A-neg. O(H)-1	64	64	128
1325278	A / O	S / NS	Neg.	Neg.	A-1 O(H)-1	A-tr. O(H)-tr.	A-tr. O(H)-neg.	A-tr. O(H)-neg.	A-neg. O(H)-tr.	A-neg. O(H)-neg.	64 64		128
834980	B / O	S / S	Neg.	Neg.	B-2 O(H)-4	B-tr. O(H)-tr.	B-tr. O(H)-tr.	B-1 O(H)-1	B-neg. O(H)-tr.	B-neg. O(H)-tr.		64	
980510	A / O	NS / S	Neg.	Neg.	A-neg. O(H)-4	A-neg. O(H)-2	A-neg. O(H)-tr.	A-neg. O(H)-neg.	A-neg. O(H)-neg.	A-neg. O(H)-neg.	64		128
2272529	A / O	S / S	A-tr.	Neg.	A-2 O(H)-16	A-tr. O(H)-1	A-tr. O(H)-tr.	A-1 O(H)-tr.	A-neg. O(H)-neg.	A-neg. O(H)-neg.	64		128

*S, Secretor. NS, Nonsecretor.
†Control for A and O(H), Blood Group Substances A and B (Merck Sharp and Dohme). Control for B, Human B saliva.

amniotic fluid than it was in her own serum. When the fetus was a secretor, the concentration of its blood group substance was greater in the decidua vera than it was in the fetal serum. Also, in these heterospecific cases, the maternal antigen was not found in the fetal circulation (cord serum) or in the fetal secretions, and vice versa. Whenever maternal antigen was found in the amniotic fluid it was also found in the stomach aspirations of the infant.

Comment

The most interesting finding in this study was the presence of maternal antigen in fetal tissue and vice versa. Since the secretions and blood of the infant do not contain the maternal antigen (in maternal-fetal heterospecificity) this would imply that the maternal antigen is passing directly through the membranes into the amniotic fluid. There are two possible sources of maternal antigen, the maternal serum and the uterine glands. If it is coming from the serum, then it is being concentrated in the amniotic fluid. The uterine glands seem a more likely source for the group substance. Even repeated accidental breaks of maternal blood through the membranes would not explain a greater concentration of antigen in the amniotic fluid. It is reasonable to expect that when the mother is a secretor the uterine glands will secrete the group substance just as all the other body glands do.

Since secretors who are group A or B contain in their secretions a substance that will inhibit anti-H (Ulex), the titers shown in Tables II and III for the solutions belonging to group O fetus or mother may represent the combined product of both mother and fetus: that is, when there is a combination where either mother or fetus is group O and the A or B partner is a secretor, then the O(H) inhibition titers may be a sum of the titers of mother and fetus.

The observation by Reich and Witebsky[2, 3] that the decidua basalis usually has less antigen than the decidua vera has been confirmed. In their study, group substance was never found in the villi; however, in this study, group substance was found in the villi in very low titer. Reich and Witebsky stated that their inability to demonstrate group substance in the villi was due to an enzyme originally described by Schiff.[4, 5]

Hubinont[13] also suggests that the maternal agglutinogen can traverse the membranes directly from the uterine wall to the amniotic fluid without necessarily passing through the placenta. Brambell[14] has shown in rabbits that antibodies can pass through the fetal membranes. He has demonstrated specific antibodies in the stomach and amniotic fluid of rabbit fetuses where none could be found in the fetal circulation.

In the transfer of materials across the placenta four mechanisms have been implicated: the diffusion mechanism; active cellular transfer of materials; transfer of intact plasma particles by pinocytosis; and pathological leaks.[27] To explain the passage of maternal leukocytes and spirochetes across the placenta, additional mechanisms have been invoked. Which modus operandi is involved in the transfer of blood group substance across the M-F barrier is a matter of conjecture.

Thus one does not have to postulate a seepage of red cells across the M-F barrier to explain how the antigen gains access to the other side. If the process

is a dynamic one proceeding throughout pregnancy, then, although the amount of group substance passing through at any one point is small, when the entire surface area of the membranes is considered, the amount of antigen passing through becomes significant. If this is some sort of vague "imbibing and seepage through" of the antigen, then it is a glycoprotein with a fairly large molecular weight which is doing so. Apparently whether or not the antigen (in detectable amounts) will pass across the membranes depends on the concentration of the substance. The concentration of the antigen is in turn dependent on the secretor status of the respective mother or fetus.

The blood group substances A, B, and O(H) are composed of carbohydrate and polypeptide,[15, 16, 17] and are referred to as mucopolysaccharides.[18, 19, 20] The molecular weights as determined by sedimentation and diffusion constant measurements are as follows: A-260,000; B-1, 800,000; O(H)-320,000.[21, 22] It is generally taught that substances with a molecular weight under 1,000, with certain exceptions, pass through the placenta by simple diffusion[23] and tend to assume equal concentrations on both sides of the placental barrier. Substances of larger molecular weight such as the plasma proteins (68,000 to 200,000) do not as a rule traverse the human placenta. It is generally accepted that antibodies do regularly pass across the placenta. The antibodies are believed to be gamma globulins with a molecular weight of 103,000 to 175,000.[24, 25, 26]

Fig. 1 is a schematic presentation of the possible pathways the blood group substance can take in crossing the M-F barrier. The arrows in both directions imply that the antigen can move in both directions. It is to be understood that the passage of group substance as shown in this diagram is inferred from and not proved by the findings in this report. It seems clear that this work suggests that the membranes represent an additional route for exchange of substances between mother and fetus. The usual implications of the term "human placental barrier" stress only the trophoblastic cell layer of the chorionic villi with the maternal and fetal circulation on either side of it. Since this definition does not include the amniotic membrane, the membranous chorion, the decidua vera, and the decidua basalis, and since all these tissues appear to be implicated in the transfer of substance from mother to fetus, I prefer the term M-F barrier. Certainly, the fetal membranes deserve far more attention in the future than they have received in the past.

Clinical Implication

The findings in this study appear to offer an explanation as to why A-B-O hemolytic disease, in contrast to Rh hemolytic disease, is so commonly seen in the first pregnancy. Since the Rh substance is found primarily on the red blood cell, sensitization of the mother can occur only after sufficient whole blood from the fetus has leaked across the placenta (a not too common occurrence even in the latter phase of gestation); thus the first infant, although capable of sensitizing the mother, will escape the disease, since sensitization will begin to take place only in the terminal phase of the gestation. In A-B-O hemolytic disease, however, if the first infant is a secretor, there is theoretically

ample opportunity for the fetal blood group substance in the amniotic fluid to traverse the membranes and thus sensitize the mother. If this is so, then one would expect to find: (a) that the infant is a secretor in almost all cases of A-B-O hemolytic disease occurring in a first pregnancy; (b) that most of the affected infants are secretors; and (c) that when an affected infant is a nonsecretor it would probably have an elder sibling of the same blood group who was a secretor. Also, a nonsecretor would tend to have less protection against the maternal antibodies and thus to be more severely affected.

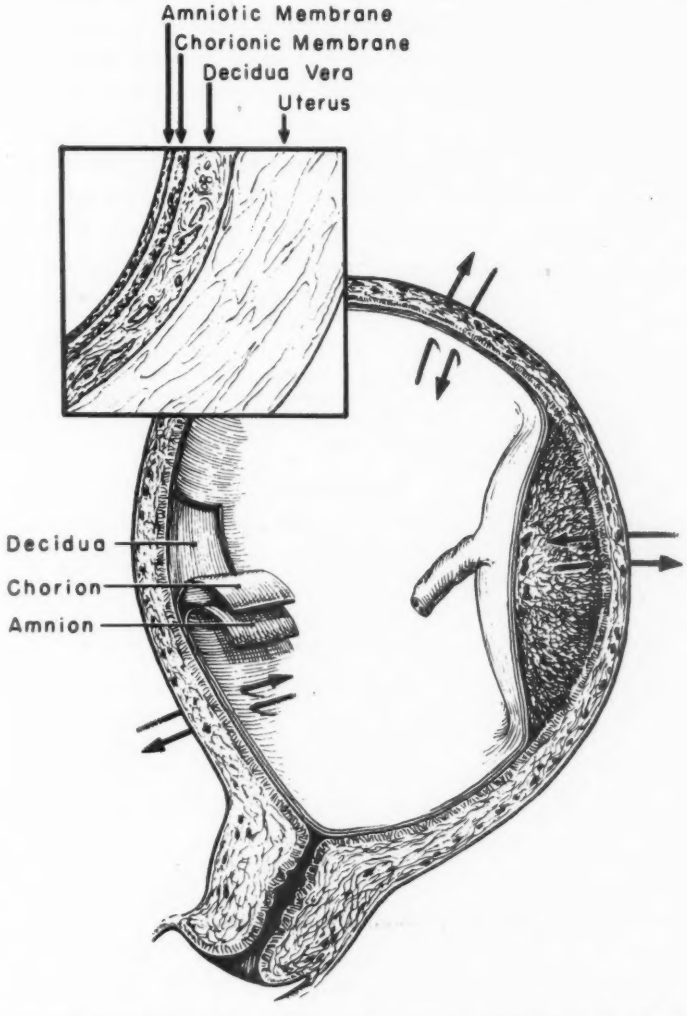

Fig. 1.—Proposed passage of blood group substance across the M-F barrier. The arrows in both directions do not signify equilibrium; they simply imply that the antigen can move in both directions directly across the membranes. The inset demonstrates the various tissues the blood group substance must traverse in passing directly from uterine wall to amniotic fluid and vice versa. (The diagram has been modified from Eastman.[23])

Summary

The placenta, membranes, and amniotic fluid obtained from 20 full-term human pregnancies were studied for the presence of A, B, O(H) blood group

substances and this in turn was related to the blood group and secretor status of the mother and infant.

1. In cases of maternal-fetal heterospecificity, only when the mother was a secretor could her blood group substance be found in the amniotic fluid and fetal membranes as well as in the decidua basalis and decidua vera. The concentration of the maternal antigen was greater in the amniotic fluid than it was in the maternal serum. Also the maternal antigen was not found in the fetal circulation (cord serum) or in the fetal secretions.

2. In cases of maternal-fetal heterospecificity, only when the fetus was a secretor could the fetal antigen be found in the decidua vera and decidua basalis as well as in the amniotic fluid, membranes, and occasionally the placental villi. The concentration of fetal antigen was greater in the decidua vera than it was in the fetal serum.

These and other findings suggest that the blood group substances A, B, and O(H), despite their large molecular weight, do traverse the membranes directly from the uterine wall to the amniotic fluid and vice versa. It is also suggested that when the mother is a secretor the source of antigen is the uterine glands. The clinical implications of these findings have been discussed.

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References

1. von Oettingen, K., and Witebsky, E.: München. med. Wchnschr. **75**: 385, 1928.
2. Reich, H.: Ztschr. Immunitätsforsch. u. exper. Therap. **77**: 449, 1932.
3. Witebsky, E., and Reich, H.: Klin. Wchnschr. **11**: 1960, 1932.
4. Schiff, F., and Weiler, G.: Biochem. Ztschr. **235**: 454, 1931.
5. Schiff, F., and Saski, H.: Klin. Wchnschr. **11**: 1426, 1932.
6. Hartmann, G.: Group Antigens in Human Organs, Copenhagen, 1941, Ejnar Munksgaard.
7. Morgan, W. T. J., and Watkins, W. M.: Brit. J. Exper. Path. **29**: 159, 1948.
8. Boyd, W. C.: J. Immunol. **65**: 281, 1950.
9. Cazal, P., and Lalaurie, M.: Acta haemat. **8**: 73, 1952.
10. Renkonen, K. O.: Ann. med. exper. et biol. Fenniae **26**: 66, 1948.
11. Boyd, W. C., and Shapleigh, E.: Blood **9**: 1195, 1954.
12. Wiener, A. S.: Blood Groups and Transfusion, ed. 3, Springfield, Ill., 1943, Charles C Thomas, Publisher.
    Wiener, A. S.: In press.
13. Hubinont, P. O.: Personal communication.
14. Brambell, F. W. R., Hemmings, W. A., Henderson, M., and Rowlands, W. T.: Proc. Roy. Soc., London, s.B. **137**: 239, 1950.
15. Kabat, E. A.: Blood Group Substances, New York, 1956, Academic Press, Inc.
16. Landsteiner, K., and Harte, R. A.: J. Exper. Med. **71**: 551, 1940.
17. Morgan, W. T. J., and King, H. K.: Biochem. J. **37**: 640, 1943.
18. Meyer, K.: Advances in Protein Chem. **2**: 249, 1945.
19. Stacey, M.: Advances in Carbohydrate Chem. **2**: 162, 1946.
20. Morgan, W. T. J.: Proc. Roy. Soc. Med. **46**: 783, 1953.
21. Kekwick, R. A.: Biochem. J. **46**: 438, 1950; **50**: 471, 1950; **52**: 259, 1952.
22. Caspari, E. A.: Biochem. J. **57**: 295, 1954.
23. Eastman, N. J.: Williams Obstetrics, ed. 11, New York, 1956, Appleton-Century-Crofts, Inc.
24. Polano, O.: Experimentelle Beitrage zur Biologie der Schwangerschaft, Wurzburg, 1904, H. Sturtz.
25. Polano, O.: Ztschr. Geburtsh. u. Gynäk. **53**: 456, 1904.
26. Plass, E. D., and Matthew, C. W.: Bull. Johns Hopkins Hosp. **36**: 393, 1925.
27. Flexner, Louis B., editor: Gestation: Transactions of the First Conference, New York, 1955, Josiah Macy, Jr., Foundation.

DIABETES MELLITUS AND PREGNANCY (1932-1957)

An Analysis of the Factors Responsible for the Improved Fetal Salvage During the Current Decade

PAUL PEDOWITZ, M.D., AND EDMUND L. SHLEVIN, M.D.,
BROOKLYN, N. Y.

(From the Departments of Obstetrics and Gynecology and Medicine at the Jewish Hospital of Brooklyn, and the Departments of Obstetrics and Gynecology and Medicine, State University of New York College of Medicine, Downstate Medical Center and the Kings County Hospital)

AS A result of analyses of the cases of diabetes complicated by pregnancy from 1932 to 1950,[1] a new approach to the management was evolved in 1950 and put into practice at the Jewish Hospital of Brooklyn.

These principles were: (1) more intensive prenatal supervision; (2) better patient cooperation through education; (3) premature delivery by the method deemed most feasible; and (4) treatment of the newborn as a premature.

Review of the data of the first 4 years showed a marked reduction in fetal wastage.[2] Since then, sufficient time has elapsed to enable us to determine whether the good results were merely fortuitous or actually a reflection of the new approach.

The purpose of this paper is twofold, namely, to compare the earlier series (1932-1949) with the current one (1950-1957, inclusive), and to emphasize again that the early recognition and treatment of the patient with unsuspected diabetes will reduce the fetal loss in this group.

TABLE I. TIME OF FETAL LOSS IN 360 VIABLE PREGNANCIES IN DIABETIC PATIENTS

SERIES	NO. OF CASES	TIME OF FETAL LOSS			TOTAL INFANT LOSS	
		ANTE PARTUM	INTRA PARTUM	NEONATALLY	NO.	%
Early	141	13	10	8	31	22.0
Current	219	6	1	12	19	8.7

Material

From 1932 through 1949,* there were 141 viable pregnancies in diabetic patients, and from 1950 to Dec. 31, 1957,† 219.

In the earlier series, the fetal mortality was 22 per cent and in the current one 8.7 per cent (Table I). If Group A cases are excluded from the

*Hereafter designated as "earlier series."
†Hereafter designated as "current series."

present series, the over-all fetal mortality is increased only slightly to 8.9 per cent.

A glance at Table II shows that the second series is comparable and the improvement in fetal salvage is evident in every group. Therefore the good end results may be attributed to our latest method of management.

TABLE II. FETAL LOSS IN 360 VIABLE PREGNANCIES IN DIABETIC PATIENTS

CLASSIFICATION*	EARLY SERIES		CURRENT SERIES	
	NO. OF CASES	PERINATAL LOSS (%)	NO. OF CASES	PERINATAL LOSS (%)
A	0	--	27	7.4
B	79	19.0	121	9.9
C	51	25.5	52	3.8
D	8	25.0	13	15.4
E	2	50.0	0	0.0
F	1	0.0	6	16.7
Total	141	22.0	219	8.7

*Group A, Abnormal Glucose Tolerance Curve.
Group B, *Onset* at age 20 or more, or *duration* 1-9 years.
Group C, *Onset* at 10-19 years of age, or *duration* 10-19 years.
Group D, *Onset* prior to age of 10, or *duration* 20 or more years, or diabetic retinopathy.
Group E, Atherosclerosis of pelvic vessels.
Group F, Diabetic nephropathy.

TABLE III. COMPLICATIONS OF PREGNANCY AND DELIVERY IN 360 VIABLE PREGNANCIES IN DIABETIC PATIENTS

COMPLICATION	EARLY SERIES			CURRENT SERIES		
	NO. OF CASES	FETAL LOSS		NO. OF CASES	FETAL LOSS	
		NO.	%		NO.	%
Acidosis	22	5	22.8	38	5	13.2
Acidosis and pre-eclampsia	1	1	100.0	3	0	0.0
Pre-eclampsia	24	4	16.7	18	1	5.6
Polyhydramnios	4	1	25.0	14	0	0.0
Impacted shoulders	18	0	0.0	10	0	0.0
Erb's palsy	8			5		
Third-degree tear	1	0	0.0	1	0	0.0
Cerebral hemorrhage	0	0	0.0	1	1	100.0
Precipitate labor	0	0	0.0	1	1	100.0
Premature separation of placenta	0	0	0.0	1	1	100.0
Postpartum hemorrhage	0	0	0.0	1	0	0.0
Fractured humerus	1	0	0.0	0	0	0.0
Fractured spine	1	1	100.0	1	1	100.0
Fractured skull	3	3	100.0	0	0	0.0
Accidental perforation of fetal skull	1	1	100.0	0	0	0.0
Separation of maternal pelvis	0	0	0.0	1	0	0.0
None	65	15	23.1	129	9	7.0
Total	141	31	22.0	219	19	8.7

Management

More Adequate Prenatal Care.—Meticulous prenatal care combined with better patient cooperation has resulted in the earlier recognition and prompt treatment of ketosis and pre-eclampsia. As a result of the daily testing of the urine by the patient for acetone, it is rare today to encounter clinical keto-acidosis. Although Table III shows a similar incidence of acidosis in both series, only 5 of the 41 cases in the current group represent clinical acidosis, whereas the other 36 merely showed early chemical ketonuria. In the earlier series all

the cases were in severe clinical acidosis when first recognized. In the present group the only patients who exhibited progressive ketosis were those who failed to cooperate, or in whom the diabetes was not discovered early.

As a result of a poor fetal salvage in the management of toxemia prior to 1948, it was decided to interrupt pregnancy within 72 hours after recognition of the pre-eclampsia, if the fetus was viable. Thus, in the 36 cases treated by this regime, only one fetus was lost. All the fetal deaths in the earlier series occurred while the patients were being treated expectantly (Table IV). Thus, although meticulous care did not decrease the incidence of toxemia to that found in the nondiabetic, it afforded the opportunity for earlier recognition and prompt treatment with resulting improvement in fetal survival. The value of more adequate prenatal care has been stressed by most investigators.[3-5]

TABLE IV. TREATMENT AND PERINATAL LOSS IN PRE-ECLAMPSIA COMPLICATING VIABLE PREGNANCIES IN DIABETIC PATIENTS

MANAGEMENT AFTER DIAGNOSIS	EARLY SERIES		CURRENT SERIES	
	NO. OF CASES	PERINATAL LOSS (%)	NO. OF CASES	PERINATAL LOSS (%)
Termination within 72 hours	15	0.0	21	4.8
Expectant therapy	10	50.0	0	0.0
Total	25	20.0	21	4.8

Premature Delivery.—More adequate prenatal care with improved patient cooperation and delivery of all cases in the current series prior to the thirty-eighth week of gestation, has reduced the antepartum fetal loss by over 50 per cent (Table V). This has not been accompanied by a corresponding increase in the neonatal death rate. The danger of death in the newborn delivered during the interval of 14 to 28 days prior to the estimated date of confinement is less than the danger of intrauterine death if pregnancy continues beyond the thirty-seventh week of gestation. More than 50 per cent of the antepartum fetal deaths in the earlier series occurred after this period. In our zeal for obtaining a live infant, we must bear in mind that delivery should not be effected prior to the thirty-sixth week, unless there is complicating pre-eclampsia, progressive or repeated bouts of acidosis, or any other obstetrical complication requiring immediate delivery. In these instances, the infant does better in the incubator than in the toxic environment of the mother. In uneventful cases, the additional complication of prematurity can only increase the fetal wastage.

TABLE V. TIME OF OCCURRENCE OF 19 INTRAUTERINE DEATHS IN 360 VIABLE PREGNANCIES IN DIABETIC PATIENTS

SERIES	TOTAL CASES	WEEK OF GESTATION						
		31	34	35	36	39	40	42
Early	13	0	0	1	4	3	4	1
Current	6	1	3	0	2	0	0	0

Mode of Delivery.—No categorical statement can be made as to what constitutes the ideal mode of delivery for the pregnant diabetic patient. The important thing is to utilize the method which will best effect premature delivery with minimal deleterious results to the fetus. If induction of labor with vaginal delivery is feasible, it should be utilized; otherwise cesarean section should be performed.

The mode of delivery and fetal loss associated with each type are summarized in Table VI. The increased fetal risk associated with breech delivery would indicate that infants in this presentation are best delivered in most instances by the abdominal route. In the earlier series, 70.2 per cent of the deliveries were per vaginam. There were 6 intrapartum fetal deaths during the first stage of labor and 6 others as a result of traumatic deliveries. Three of these occurred neonatally.

TABLE VI. MODE OF DELIVERY IN 360 VIABLE PREGNANCIES IN DIABETIC PATIENTS AT THE JEWISH HOSPITAL OF BROOKLYN

	EARLY SERIES			CURRENT SERIES		
	NO. OF	PERINATAL LOSS		NO. OF	PERINATAL LOSS	
MODE OF DELIVERY	CASES	NO.	%	CASES	NO.	%
Spontaneous	67	13	19.4	45	7	15.6
Low forceps	19	6	31.6	15	0	0.0
Midforceps	9	4	44.4	15	1	6.7
Assisted breech	4	3	75.0	1	1	100.0
Cesarean section	42	5	11.9	143	10	7.0
Total	141	31	22.0	219	19	8.7

In the current series there were 2 deaths due to traumatic delivery. The incidence of impacted shoulders and resultant Erb's palsy was high in both series. Thus by delivering 65.3 per cent of the patients by cesarean section in the present series, we were able to minimize the fetal deaths due to traumatic delivery and labor. Slightly more than one-third of the primary sections were performed because of an unfavorable cervix (Table VII). More than half of the remainder were performed because of a previous fetal loss or traumatic delivery. The rest were done for obstetrical indications.

TABLE VII. INDICATIONS FOR CESAREAN SECTION IN VIABLE PREGNANCIES IN DIABETIC PATIENTS

INDICATION	EARLY SERIES	CURRENT SERIES
Previous section	14	57
Disproportion	5	4
Bad obstetrical history	0	25
Previous traumatic delivery	0	8
Pre-eclampsia	18	12
Acidosis	0	5
Prolonged labor	0	1
Unfavorable cervix	5	31
Total	42	143
Incidence	29.8%	65.3%

TABLE VIII. CAUSE OF NEONATAL MORTALITY IN 360 VIABLE PREGNANCIES IN DIABETIC PATIENTS AT THE JEWISH HOSPITAL OF BROOKLYN

CAUSE	EARLY SERIES	CURRENT SERIES	GRAND TOTAL
Traumatic delivery	3	2	5
Congenital anomaly	1	1	2
Aspiration	2	3	5
Hyaline membrane	1	4	5
Rh incompatibility	1	0	1
Accidental perforation of rectum	0	1	1
Hemorrhagic disease of the newborn	0	1	1
Total	8	12	20

Neonatal Fetal Loss.—With the marked reduction in antepartum and intrapartum fetal deaths, and the almost universal adoption of premature delivery,

an increase in the percentage of infants lost during the neonatal period would have been anticipated. In the earlier series 6.8 per cent of the infants born alive were lost during this period, as compared to 5.7 per cent in the current series. As noted in Table VIII, traumatic delivery still accounted for one-sixth of the fetal loss in the present series. The fetal loss due to hyaline membrane disease was not as great as one might have expected from the time and method of delivery of these babies. The better quality of care in the premature nursery has prevented unnecessary fetal deaths due to aspiration during feeding.

The Patient With Unsuspected Diabetes.—In recent years it has become more apparent that abnormal carbohydrate metabolism in pregnancy is associated with a high fetal wastage.[6-8] The infants born to these mothers have embryopathology similar to those born of mothers known to have diabetes.[6, 9-11] It is only by early recognition and treatment of these patients as diabetic that one can improve the fetal salvage in this group.

A suspicion that an abnormal carbohydrate state is present can be gleaned from a poor obstetrical history, or from the current pregnancy. This suspicion becomes even greater if there is a familial history of diabetes. It can be confirmed or negated by performing glucose tolerance tests, repeated if necessary during each trimester.

Unexplained intrauterine deaths, recurrent episodes of pre-eclampsia, excessive-sized infants (4,000 grams or more) or a baby large for the period of gestation, habitual abortions, and glycosuria should lead to an investigation of the possibility of diabetes.

Reliance should not be placed on fasting blood sugar determinations and urine specimens for the diagnosis of diabetes, for they may be normal in many mild cases. Postprandial specimens are more informative.

The diabetes, detected by these measures, should not be regarded as innocuous and must be watched carefully. Disturbance of carbohydrate metabolism as pregnancy progresses may remain relatively static or increase in severity. Failure to adapt therapy to the changing status of the diabetes may result in a poor fetal outcome, as is illustrated in the following case report:

E. R., No. 186508, a 31-year-old para i-0-i-i, was first admitted to the prenatal clinic at the Jewish Hospital of Brooklyn on Aug. 16, 1955. Her last menses was May 10, 1955, and estimated date of confinement was Feb. 17, 1956. Her first pregnancy in 1954, complicated by pre-eclampsia, ended in the thirty-seventh week of gestation with the spontaneous delivery of a 3,000 gram living infant. In 1955 she had an early spontaneous abortion. At the initial clinic visit, glycosuria was detected and a familial history of diabetes was then elicited. A glucose tolerance test done on Aug. 30, 1955, showed an abnormal curve (Table IX). Thereafter there was no glycosuria noted at her prenatal visits. On Nov. 15, 1955, she was admitted to the hospital for evaluation of her diabetic status. She was placed on a calculated diet. Insulin was not deemed necessary. The patient was discharged and instructed to test her urine daily for sugar and acetone and return to the clinic at weekly intervals, or immediately if she exhibited acetonuria.

Thereafter the patient did not return to the clinic despite several requests until Jan. 12, 1956. At this visit she showed marked glycosuria and acetonuria. Incidentally, she kept records of her urine from the time of her discharge and they showed daily ketonuria. She was admitted to the hospital and the carbon dioxide was 16.5 mEq. per liter. She was placed on insulin and the ketoacidosis was brought under control. On Jan. 16, 1956, an emergency cesarean section was performed because of absence of fetal movements and questionable heart sounds. A 3,360 gram markedly edematous moribund infant was delivered, that died 14 hours later.

It is our feeling that the poor fetal outcome can be attributed to inadequate diabetic management and lack of patient cooperation. Insulin therapy should have been employed much earlier.

TABLE IX. GLUCOSE TOLERANCE TESTS

	DATE AND GESTATION AGE					
	8/30/55 16 WEEKS		11/15/55 26 WEEKS		1/19/56 3 DAYS POST PARTUM	
	BLOOD	URINE	BLOOD	URINE	BLOOD	URINE
Fasting	119	Negative	191	Negative	125	Negative
½ hour	205	Trace	274	Negative	197	Negative
1 hour	252	2 plus	325	4 plus	270	4 plus
2 hours	171	No specimen	320	4 plus	247	4 plus
3 hours	122	3 plus	262	4 plus	140	4 plus

Comment

The improved fetal salvage in the pregnant diabetic patient during the present era can be attributed in large measure to better management and patient cooperation. This has reduced the hazard of antepartum fetal death.

Most investigators agree that premature delivery should be effected in the pregnant patient with diabetes. In the zeal to accomplish premature delivery, many are delivering these patients earlier and earlier. This has resulted in an increase in neonatal deaths. It has been our observation that over three-fourths of the antepartum fetal deaths occurred when pregnancy was accompanied by recurrent episodes of ketoacidosis and pre-eclampsia. Therefore, in the uncomplicated case, the danger of intrauterine death is not as great as one might be led to expect. As a result, the patients with uncomplicated cases in the present series were delivered 18 to 22 days prior to the estimate date of confinement. The neonatal death rate at this period of gestation is practically identical with that obtained at term, and probably accounts for the small number of neonatal deaths in this series. If pregnancy is terminated earlier, the neonatal death rate rises sharply as prematurity increases. Thus a diabetic infant delivered 6 weeks prior to term and weighing 3,000 grams is probably identical physiologically with the premature offspring of the nondiabetic mother weighing 1,500 to 2,000 grams or less. Thus, premature delivery prior to 28 days before term is indicated only in the complicated case wherein the risk of intrauterine death is greater than the anticipated neonatal loss.

It would be advantageous to express the optimum time of delivery in regularly menstruating women as the number of days prior to the estimated date of confinement. In those who menstruate irregularly, if the time of conception cannot be accurately determined either by an examination early in pregnancy, or by laboratory test, it is best to gauge the time for delivery by the estimated size of the fetus. A small fetus would indicate that delivery should be deferred for one or more weeks. If this concept had been followed, it might have prevented one of our neonatal deaths due to marked prematurity.

By the increased utilization of cesarean section, there has been a marked decrease in intrapartum fetal deaths. At present we feel that elective cesarean section is the best method to accomplish delivery when the cervix is unfavorable. Whenever it can be conclusively shown that the cervix can be ripened and delivery accomplished with intravenous Pitocin, without any increase in perinatal loss for these diabetic mothers, then induced vaginal delivery will be acceptable. Today this is not always the case.

If intravenous Pitocin fails to accomplish its desired effect, or inertial labor ensues, or if midpelvic plane arrest occurs, cesarean section should be performed. Breech presentation may best be delivered abdominally.

The high fetal mortality associated with abnormal carbohydrate metabolism is preventable in most instances. Prospective rather than retrospective diagnoses will result in a marked improvement in fetal salvage. The early recognition and proper management of these patients as diabetics are essential to accomplish this. Diet alone may be sufficient, but in the vast majority of cases insulin will have to be used in order to maintain carbohydrate metabolism as close to normal as possible. The patient who may not require insulin when the diabetes is first recognized may need it as pregnancy advances. The need for insulin may be determined by symptomatology, urinary findings, and periodic postprandial blood sugar estimations. Failure to appreciate this may result in increased fetal mortality. This is well documented in the case report cited earlier.

The time and method of delivery of the patient with an abnormal glucose tolerance curve (Class A) is dependent upon the past obstetrical history and course of the current pregnancy (Table X). Premature delivery 14 to 21 days prior to term is indicated in all patients with a poor obstetrical history, or in those with episodes of recurrent acidosis, polyhydramnios, or those in whom a flat plate of the abdomen shows a marked halo around the fetal skull. If pre-eclampsia develops, delivery should be effected within 72 hours following its recognition. In all other patients, labor should be induced as soon as the cervix is favorable. This can be accomplished in the absence of cephalopelvic disproportion by amniotomy and Pitocin stimulation. Breech presentation and excessive-sized infants are best delivered by cesarean section.

TABLE X. MODE OF DELIVERY AND INDICATIONS FOR CESAREAN SECTION IN 27 CASES OF GROUP A DIABETIC PATIENTS

		NO. OF CASES	FETAL LOSS
Induction of labor (by amniotomy and intravenous Pitocin) with spontaneous delivery		11	1
Spontaneous labor and delivery		6	0
Cesarean section		10	1
Indication for cesarean section:			
Cephalopelvic disproportion	2		
Poor obstetrical history	2		
Pre-eclampsia	2		
Unripe cervix	2		
Previous cesarean section	2		
Total		27	2

Improvement in fetal salvage can be anticipated as a result of further education. In the current series, 11 infant deaths were preventable. The accidental perforation of the rectum by a thermometer was a rare accident. Perhaps utilization of cesarean section would have prevented 2 fetal deaths due to traumatic vaginal delivery. Poor patient cooperation resulted in the loss of 2 fetuses from acidosis. The occurrence of 3 aspiration deaths vividly points out that gastric aspiration in the newborn should be performed by the most experienced individual. As noted previously, too early delivery and inadequate management of diabetes accounted for 2 additional deaths. Finally, earlier diagnosis of diabetes might have prevented one of the intrauterine fetal deaths.

Summary

1. A total of 360 viable pregnancies in diabetic patients from 1932 to the present are reviewed.

2. The viable fetal loss in the earlier series (1932 to 1949) was 22 per cent and in the current series (1950 to date) was 8.7 per cent.

3. The method of management responsible for this improvement is presented.

4. The patient with an abnormal glucose tolerance curve during pregnancy should be treated as a diabetic.

5. Further education and cooperation of patients are necessary to improve fetal salvage in the diabetic.

6. In the uncomplicated case, termination of pregnancy more than 28 days prior to the estimated date of labor will result in an increased fetal mortality.

References

1. Pedowitz, P., and Shlevin, E. L.: Bull. New York Acad. Med. **28:** 440, 1952.
2. Pedowitz, P., and Shlevin, E. L.: AM. J. OBST. & GYNEC. **69:** 395, 1955.
3. Pedersen, J.: Acta endocrinol. **15:** 282, 1954.
4. Hagbard, Lars: Acta obst. et gynec. scandinav. **35:** Supplement 1, 154, 1956.
5. Nelson, H. B., Gillespie, L., and White, P.: Obst. & Gynec. **1:** 219, 1953.
6. Pedowitz, P., and Shlevin, E. L.: Obst. & Gynec. **9:** 524, 1957.
7. Carrington, E. R., Reardon, H. S., and Shuman, C. R.: J. A. M. A. **166:** 245, 1958.
8. Hoet, J. P.: Diabetes **3:** 1, 1954.
9. Jackson, W. P.: Lancet **2:** 625, 1955.
10. Carrington, E. R., Shuman, C. R., and Reardon, H. S.: Obst. & Gynec. **9:** 664, 1957.
11. Zetterstrom, R., and Aberg, B.: Acta paediat. **44:** 1, 1955.

UNSUSPECTED "PREDIABETIC STATE" AND PREGNANCY

LUCIANO S. J. SOTTO, M.D.,* DENNIS P. HEIMBACK, M.D., AND ALLAN W. SIEGNER, M.D., BUFFALO, N. Y.

(From the Department of Obstetrics and Gynecology, Millard Fillmore Hospital)

ABNORMAL glucose tolerance in pregnancy and the early puerperium, in the absence of overt diabetes, has been interpreted in recent years as being indicative of preclinical diabetes or a prediabetic state. Some investigators[1, 2] have shown that such a condition in pregnant women, when unrecognized, is accompanied by a high fetal mortality, the rate ranging from 20 to 30 per cent. They have shown also that when the condition is recognized sufficiently early in pregnancy and appropriate treatment instituted, the fetal mortality is no higher than in normal pregnant women. Early diagnosis, therefore, would be most desirable for proper management of this condition.

Our interest in this subject began in November, 1956, with the presentation by Carrington and her associates[3] on the prediabetic state during pregnancy, emphasizing the need for early diagnosis. The present study started in December, 1956, with the following purposes: (1) to determine the incidence of unsuspected abnormal glucose tolerance in (a) those women in whom there were one or more factors suggestive of a prediabetic state and (b) in perfectly normal women in the immediate puerperium, and (2) to determine the perinatal mortality in patients with unrecognized abnormal glucose tolerance.

Materials and Method

From Dec. 1, 1956, through Oct. 31, 1957, glucose tolerance tests were performed in the immediate puerperium on 300 patients at the Millard Fillmore Hospital in Buffalo, New York, divided into a study group (198 patients) and a control group (102 patients). The study group comprised patients on whom the test was done because of the presence of one or more factors suggestive of prediabetes; namely, oversize babies (9½ pounds and over), family history of diabetes, previous babies weighing over 9 pounds, repeated abortions, unexplained fetal deaths, and persistent glycosuria. The control group was studied concurrently and was selected on the basis of the following: (1) that none of the indications for the study group should be present; (2) that they should be at term; (3) that labor, delivery, and the immediate puerperium (24 hours) should be uncomplicated; (4) that they should not be obese; (5) that they should not have any obvious endocrine abnormality; and (6) that their babies should be perfectly normal and healthy.

*Now at Roswell Park Memorial Institute, Buffalo, N. Y.

The youngest patient in the study group was 14 years of age, the oldest, 42; in the control group, the youngest was 18 and the oldest 41. The majority of the patients in both groups were multiparas, the ratio of multiparas to primiparas being slightly higher in the study group. All but 5 patients were delivered at term; of these 5, 2 were delivered at the twenty-eighth and thirty-fourth weeks, respectively, and 3 at 42 weeks and over.

All the glucose tolerance tests were done from 24 to 72 hours post partum except in 9 cases in which they were done from 72 to 96 hours after delivery. Patients who were known to have diabetes, as well as patients with a fasting blood sugar level of over 120 mg. per 100 c.c., were excluded from the study. All blood sugar levels were determined by the Folin-Wu method. A 2 hour blood glucose level of 120 mg. per 100 c.c. and over was considered abnormal, following the criterion of Carrington and associates.[2] They have considered these patients as prediabetics.

Since all the tests were done in the immediate puerperium, any abnormal result was regarded as indicative of the "prediabetic state," not suspected during the pregnancy. It is conceivable that we may have missed some cases, as it is known that this condition reverts to normal soon after delivery. It is also possible that the effects of labor, starvation, and dehydration may be reflected in some of the tests when done soon after delivery, but these factors should be the same in the control series.

The results in the entire series are classified into three categories, depending on the blood glucose level at the end of 2 hours, as follows: (1) normal—blood glucose level up to 119 mg./100 c.c.; (2) suspicious of prediabetes—120 to 139 mg., and (3) probable prediabetes—140 mg. and over (after Carrington and co-workers). No attempt was made to subdivide the group whose 2 hour blood glucose level exceeded 140 mg. per 100 c.c. into prediabetes (140 to 169 mg.) and gestational diabetes (170 mg. and over) as Carrington and her associates did.

Results

Incidence of Abnormal Glucose Tolerance Curve.—Table I is a comparison of results of the glucose tolerance test in both groups. Of 198 patients in the study group, 42, or 21.2 per cent, had a "prediabetic curve," and 50, or 25.3 per cent, a curve "suspicious of prediabetes"—or an incidence of 46.5 per cent abnormal glucose tolerance curves in the study group.

TABLE I. COMPARISON OF TWO-HOUR BLOOD GLUCOSE LEVEL IN BOTH GROUPS

GROUP	TOTAL CASES	NORMAL (UP TO 119 MG./100 C.C.)		SUSPICIOUS (120-139 MG.)		PREDIABETIC (140 MG. AND OVER)	
		NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL
Study group	198	106	53.5	50	25.3	42	21.2
Control group	102	82	80.4	12	11.7	8	7.9

In the control group of 102 normal patients, 8, or 7.9 per cent, showed a "prediabetic curve," and 12, or 11.7 per cent, a curve "suspicious of prediabetes"—or an incidence of 19.6 per cent abnormal curves in the control series. Thus the incidence of abnormal curves in the study group was approximately two and one-third times that of the control group. The difference in the incidence of abnormal glucose tolerance in these two groups is probably significant enough to suggest a diagnosis of prediabetic state on this basis alone, but certainly is not conclusive.

Labor and Delivery.—The majority, or 83.2 per cent, of the patients in the entire series had spontaneous labor, and 16.8 per cent had either an induced or assisted labor. Patients who were delivered by cesarean section were not included in the study since it was deemed that the intravenous glucose these patients received in the immediate postoperative period interfered with the test. This was later confirmed in a control series of normal patients delivered by cesarean section. All the inductions in this series were purely elective, done for reasons other than medical or obstetric. Only 2 patients had prolonged labor (18 hours and over), one in the study group and one in the control group. The majority of the patients were given nitrous-oxide-ether and oxygen anesthesia. These data imply that unsuspected abnormal glucose tolerance during pregnancy, suggestive of a prediabetic state, did not affect labor and delivery in this series.

Indications for Test in Study Group.—Table II lists the indications for which the glucose tolerance test was done, as well as its results, among the 198 patients in the study group. One hundred and sixty of the women presented only one of the indications for the test, and in 38 patients there were two or more of the indications. Oversize babies and a family history of diabetes lead the list of indications. The incidence of an abnormal curve among the mothers with oversize babies was 50.8 per cent, which is close to that found by Lund and Weese[4] (66 per cent), and among those with a family history of diabetes it was 38.4 per cent. Multiple indications were present in 38 patients, 47.4 per cent of whom had abnormal glucose tolerance.

TABLE II. INDICATIONS FOR TEST AND THE TWO-HOUR BLOOD GLUCOSE LEVELS IN STUDY GROUP: 198 CASES

INDICATIONS	NO. OF CASES	NORMAL (UP TO 119 MG./100 C.C.)		SUSPICIOUS (120-139 MG.)		PREDIABETIC (140 MG. AND OVER)	
		NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL	NO. OF CASES	% OF TOTAL
A. Single indications:							
Oversize babies (9½ pounds)	67	33	49.2	19	28.6	15	22.2
Family history of diabetes	60	37	61.6	13	21.6	10	16.8
Previous babies over 9 pounds	18	6		7		5	
Unexplained fetal death	6	5		1		0	
Repeated abortions (at least 3)	6	4		1		1	
Persistent glycosuria	3	1		1		1	
Total	160	86		42		32	
B. Multiple indications	38	20	52.6	8	21.1	10	26.3

Perinatal Mortality.—No attempt is made to compare the fetal mortality between the two groups since the women used as controls were carefully selected patients.

Table III shows the perinatal mortality in the study group according to the type of curve. It will be noted that the perinatal mortality in a group of 42 patients with a 2 hour blood glucose level of 140 mg. per 100 c.c. and over is 2.2 per cent, and in the suspicious group it is 4.0 per cent. Thus, among the 92 patients with unsuspected abnormal glucose tolerance, the perinatal mortality (corrected or uncorrected) was only 3.3 per cent, while the corrected fetal mortality among 106 patients who had normal 2 hour blood glucose levels is 3.7 per cent.

TABLE III. PERINATAL MORTALITY IN STUDY GROUP: 198 CASES

2 HOUR BLOOD GLUCOSE LEVEL (MG. PER 100 C.C.)	NO. OF CASES	GROSS PERINATAL MORTALITY		CORRECTED FETAL MORTALITY (%)
		STILLBIRTHS	NEONATAL DEATHS	
Up to 119 (Normal)	106	6*	1†	3.7
120-139 (Suspicious)	50	1	1	4.0
140 and over (Prediabetic)	42	1	0	2.2
Total	198	8	2	3.5

*Includes 2 babies below 1,000 grams.
†Anencephalic monster.

Total Fetal Loss.—Table IV shows the total fetal loss in the study group. There was a total of 595 pregnancies in this group of 198 patients. The total fetal loss (abortions, stillbirths and neonatal deaths) in 106 of these patients who had normal curves (a total of 322 pregnancies) was 12.42 per cent. Among the 50 patients whose 2 hour blood glucose level was 120 to 139 mg. per 100 c.c., the total fetal loss was 6.96 per cent, while in the 42 patients whose 2 hour blood glucose value exceeded 140 mg. per 100 c.c. the total fetal loss was 17.3 per cent. The combined total fetal loss in the group with any abnormality of the glucose tolerance curve (92 patients with 273 pregnancies), therefore, was 11.2 per cent, as compared with 12.4 per cent in the normal group, which is essentially the same.

TABLE IV. TOTAL FETAL LOSS IN STUDY GROUP: 198 CASES

2 HOUR BLOOD GLUCOSE LEVEL (MG. PER 100 C.C.)	NO. OF CASES	NO. OF PREGNANCIES	FETAL LOSS				TOTAL FETAL LOSS (% OF TOTAL PREGNANCIES)
			ABORTIONS		STILLBIRTHS AND NEONATAL DEATHS		
			NO.	%	NO.	%	
Up to 119 (Normal)	106	322	23	7.14	17	5.28	12.42
120-139 (Suspicious)	50	158	8	5.06	3	1.9	6.96
140 and over (Prediabetic)	42	115	16	13.9	4	3.4	17.3
Total	198	595					

Maternal Complications.—The maternal complications encountered in the study group are shown in Table V.

TABLE V. MATERNAL COMPLICATIONS

COMPLICATIONS	NO. OF CASES
Fever (100° F. for over 24 hours)	4
Cephalopelvic disproportion	5
Shoulder impaction	2
Abnormal presentation	2
Transverse arrest	1
Polyhydramnios	1
Toxemia	1

There was no indication that an abnormal glucose tolerance, unsuspected during the pregnancy, was associated with an increase in the maternal complication rate in this series.

Follow-up Glucose Tolerance Test.—Our experience with repeat glucose tolerance tests done late in the puerperium is in agreement with that of other

authors, namely, that, in the absence of overt diabetes, glucose tolerance in a "prediabetic" patient will return to normal after delivery.

Comment

During the preinsulin era the association of diabetes and pregnancy was accompanied by a very high maternal and fetal mortality. With the discovery of insulin the maternal mortality from diabetes and its complications decreased steadily and rapidly, so that barely a decade later diabetes as a cause of death among those women was practically eliminated. The fetal salvage, however, has remained largely unimproved, despite insulin therapy and good control of diabetes. This led to hormone and "prediabetic" studies in an attempt to determine other possible causes for the fetal loss.

It had previously been observed that maternal complications and increased fetal losses occurred among diabetic women years before the clinical diagnosis of diabetes was made, but it was not until the middle forties that actual investigations were conducted to ascertain just when and why such fetal losses were incurred. In 1944, Miller and his associates[5] studied 123 patients in whom pregnancies had occurred either before or after the onset of clinical diabetes. In this group of patients the fetal mortality remained high, whether or not they were treated with insulin; in fact it was five times the fetal mortality for nondiabetic patients, and was significantly increased up to 20 years before the onset of diabetes.

The following year, the senior author[6] studied 57 women in whom diabetes had developed after the age of 40 and compared their obstetrical histories with those of nondiabetics. He found that the fetal mortality among these diabetic women in their prediabetic years was more than 2½ times that of the nondiabetics. Subsequent studies by separate investigators, including Herzstein and Dolger,[7] Paton,[8] and Moss and Mulholland,[9] confirmed these findings. All these authors arrived at one conclusion: that the fetal loss among diabetic women during their prediabetic years was significantly increased, and more so in the 5 year period preceding the onset of clinical diabetes. This stage was regarded as the prediabetic state.

These studies suggested to later investigators that if the prediabetic state could be diagnosed before clinical diabetes develops, it might be possible to reduce the fetal wastage. Diagnosis, however, presented many difficulties, from both the laboratory and pathologic standpoints, particularly as very little was known about carbohydrate metabolism in pregnancy, interpretation of the glucose tolerance test in pregnancy, or the pathology of the newborn.

Jackson,[10] reviewing the literature in 1952, found no studies of glucose tolerance during pregnancy after a test dose of glucose. He therefore included normal antepartal and postpartal women in his study, and interpreted a glucose tolerance curve as diabetic if the 2 hour blood glucose was over 140 mg.; or if the 2½ hour level was over 130 mg. per 100 c.c., combined with either a fasting blood sugar level of over 120 mg. or a peak of over 200 mg. per 100 c.c. This was based on previously set standards. He considered a curve to be prediabetic if the 2 hour or 2½ hour blood glucose level was high but the curve was otherwise normal. This latter criterion was more or less arbitrary.

On the basis of these criteria, he found an incidence of 4.7 per cent abnormal curves among perfectly normal pregnant women and 14.2 per cent among perfectly normal newly delivered mothers. He also found 11 diabetic and 8 prediabetic patients in a group delivered of oversized babies, including 14 stillborn infants. We do not know in how many of those prediabetic patients diabetes actually developed or will develop eventually. Lund and Weese[4]

in 1953 found an 8 per cent incidence of abnormal glucose tolerance in a group of normal pregnant women. They could not determine whether these deviations were physiologic or pathologic.

From the various studies it becomes evident that (1) the origin of the term "prediabetic state" was based largely on retrospective studies of diabetic women; (2) basic studies on carbohydrate metabolism during pregnancy have not been adequate, and (3) the interpretation of what constitutes an abnormal glucose tolerance or a prediabetic state during pregnancy has been based on arbitrary standards.

Despite these almost unsurmountable difficulties, some investigators have in recent years liberalized the criteria for diagnosis of a prediabetic state during pregnancy. Pedowitz and Shlevin[1] claim that any abnormal glucose tolerance during pregnancy is diabetes in its early stage, and quote a fetal mortality rate of 20 per cent. Carrington and her associates[2, 3] have regarded a 2 hour blood glucose level of 120 mg. per 100 c.c. and over as abnormal and have considered such patients prediabetic in their calculations. In their most recent paper, a 5 year study of the prediabetic state during pregnancy, the fetal mortality in the patients who exhibited an abnormal tolerance to glucose and were treated accordingly was 2.9 per cent, while in the unsuspected (and therefore untreated) cases the fetal death rate was 30 per cent. These figures are indeed very impressive but certainly not conclusive, since their treated group was not paralleled by a comparable group of untreated patients with abnormal glucose tolerance curves during pregnancy.

Our study was limited to the cases undetected during pregnancy and therefore untreated, the so-called "unsuspected prediabetics" or "unregistered prediabetics" of Carrington and co-workers.

In our control group of 102 perfectly normal, newly delivered patients, 19.6 per cent exhibited a glucose tolerance curve that can be classified as abnormal by present standards, yet we do not know whether these are normal physiologic or true pathologic variations. Other authors have found that a certain percentage of perfectly normal antepartal and postpartal women will exhibit this type of curve without necessarily being prediabetic or diabetic. In our study group of 198 patients, 46.5 per cent can be classified as "unsuspected prediabetics," yet we do not know whether their abnormal tolerance to glucose is physiologic or pathologic or how many are true prediabetics. Only a lengthy follow-up can determine this.

The perinatal mortality in the group of so-called "unsuspected prediabetics" is 3.2 per cent, which is no higher than among the patients who had a normal curve. Also the total fetal loss (considering all pregnancies) is no higher than in the patients with normal tolerance to glucose. None of the autopsied babies in either group exhibited the so-called characteristic pathologic findings of babies of known prediabetic mothers.

These findings do not lend support to previous claims about the influence of the prediabetic state in pregnancy. We can only suggest that not all abnormal glucose tolerance during pregnancy and the early puerperium indicates a prediabetic state. A better understanding of carbohydrate metabolism during pregnancy is necessary before we can differentiate between normal and abnormal or pathologic deviations in the results of the glucose tolerance test. It seems imperative that further studies be conducted along these lines before we accept a prospective diagnosis of a prediabetic state. A liberal use of such a diagnosis will lead to unnecessary premature inductions and cesarean sections, with increased risk to both mother and baby. The psychological implication of such a diagnosis must also be considered.

Summary and Conclusions

1. Three hundred glucose tolerance tests were done in the immediate puerperium at the Millard Fillmore Hospital, in Buffalo, New York, from Dec. 1, 1956, to Oct. 31, 1957. One hundred ninety-eight patients who had one or more factors suggestive of a prediabetic state comprised the study group. One hundred two normal patients were used as controls.

2. The incidence of "unsuspected abnormal glucose tolerance" in the study group was 46.5 per cent; in the control group it was 19.6 per cent.

3. The perinatal mortality among the patients with "unsuspected abnormal glucose tolerance" was 3.2 per cent, which was no higher than among those with a normal glucose tolerance curve. The total fetal loss (including abortions, stillbirths, and neonatal deaths) in the patients with abnormal glucose tolerance curves was no higher than in the patients with normal curves.

4. A prediabetic state in pregnancy is an extremely difficult diagnosis to make merely on the basis of the glucose tolerance test and the presence of one or more factors suggestive of such a condition. Abnormal glucose tolerance in pregnancy and the early puerperium does not necessarily indicate a prediabetic state, even when other suggestive factors are present. Until more is known about the factors influencing carbohydrate metabolism in pregnancy, the diagnosis of "prediabetes" should be made with great caution.

References

1. Pedowitz, P., and Shlevin, E. L.: Obst. & Gynec. **9**: 524, 1957.
2. Carrington, E. R., Reardon, H. S., and Shuman, C. R.: J. A. M. A. **166**: 245, 1958.
3. Carrington, E. R., Shuman, C. R., and Reardon, H. S.: Obst. & Gynec. **9**: 664, 1957.
4. Lund, C. J., and Weese, W. H.: Am. J. Obst. & Gynec. **65**: 815, 1953.
5. Miller, H. C., Hurwitz, D., and Kuder, K.: J. A. M. A. **124**: 271, 1944.
6. Miller, H. C.: New England J. Med. **233**: 376, 1945.
7. Herzstein, J., and Dolger, H.: Am. J. Obst. & Gynec. **51**: 420, 1946; correction **51**: 918, 1946.
8. Paton, D. M.: Am. J. Obst. & Gynec. **56**: 558, 1948.
9. Moss, J. M., and Mulholland, H. B.: Ann. Int. Med. **34**: 678, 1951.
10. Jackson, W. P. U.: Brit. M. J. **2**: 690, 1952.

THE LEG CRAMP SYNDROME DURING PREGNANCY*

The Relationship to Calcium and Phosphorus Metabolism

JEROME ABRAMS, M.D., AND G. E. APONTE, M.D.,
PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology and the Department of Pathology of the Jefferson Medical College Hospital)

THE leg cramp syndrome during pregnancy is characterized by sudden tonic or clonic contractions of the gastrocnemius muscle associated with severe pain. This syndrome has received considerable attention since Page and Page[1] advanced the concept that the leg cramp syndrome is an expression of neuromuscular irritability. The cause of this particular type of neuromuscular irritability was referred to a relative calcium deficiency enhanced by an excessive intake of phosphorus. These authors proposed as treatment the reduction in intake of milk, the administration of phosphorus-free calcium salts (e.g., calcium lactate), and/or the adsorption of phosphorus from the gastrointestinal tract with aluminum hydroxide.

Review of Previous Work

In 1947, Robinson[2] had expressed the opinion that leg cramps were not due to increased neuromuscular irritability, but were merely muscle cramps resulting from salt depletion. Calcium lactate was found to be no more efficacious than saccharine in relieving leg cramps. Since the publication of the Pages' paper in 1953, nine pharmaceutical companies have produced and publicized prenatal vitamin-mineral supplements containing calcium lactate instead of dicalcium phosphate. One company has produced a supplement containing aluminum hydroxide in addition to calcium lactate and the conventional vitamins and minerals; this supplement has been studied by Fandrich,[3] Wolff,[4] Hawker,[5] and Gross, Wager, and Loving,[6] all of whom reported it to be efficacious in alleviating leg cramps. Recently Hardy[7] endorsed a phosphorus-free product containing calcium carbonate which cured leg cramps during pregnancy.

Shorr and Carter[8] investigated aluminum gels in the management of renal phosphatic calculi; a daily dose of at least 7 Gm. of aluminum hydroxide dried gel was necessary before a significant reduction in urinary phosphorus excretion could be detected. Moreover, serum phosphorus levels were not significantly altered by high doses of aluminum gels. Hardy was unable to demonstrate any decrease in serum phosphorus in 10 pregnant women who took calcium lactate and aluminum gel.

*Presented at a meeting of the Obstetrical Society of Philadelphia, May 2, 1957.

The Pages reported significant clinical and biochemical results in 10 pregnant women with a daily dose of 1.5 Gm. of aluminum gel combined with abstinence from dairy products. Gross, Wager, and Loving reported similar clinical and biochemical results in 10 pregnant women after administering the new vitamin-mineral supplement containing 1.5 Gm. of aluminum gel. They did not state whether their patients altered their consumption of dairy products. Wolff considered the "reduction of phosphorus intake by eliminating milk, meat, and eggs" impractical.

Although we were stimulated by the biochemical theories advanced and investigated by Page and Page and by Gross, Wager, and Loving, we were not convinced that leg cramps had been proved to be an expression of increased neuromuscular irritability. Nor were we convinced that the decreased ingestion of dairy products and the consumption of any specific type of vitamin-mineral supplement with or without aluminum hydroxide would prevent or relieve the leg cramp syndrome.

Material and Methods

Clinic patients who registered for prenatal care prior to the twenty-second week of gestation were divided into three groups on the basis of the type of medication to be administered; the patients were carefully interrogated before and during the study.

Group 1 consisted of 10 patients who received vitamin-mineral supplements devoid of calcium, phosphorus, and vitamin D. Medication was started between the fourteenth and twentieth weeks of gestation and was continued until delivery. Group 2 consisted of 8 patients who received vitamin-mineral supplements containing dicalcium phosphate and vitamin D. Medication was started between the ninth and twenty-second weeks of gestation and was continued until delivery. Group 3 consisted of 10 patients who received vitamin-mineral supplements containing calcium lactate and vitamin D. Medication was started between the eleventh and twenty-second weeks of gestation and was continued until delivery. Nineteen patients who complained of leg cramps registered for prenatal care after the twenty-second week of gestation and were placed in Group 4; no medication was administered to these patients.

It was decided not to administer aluminum hydroxide because a daily dose of 7 Gm. (the minimum amount recommended for significant adsorption of phosphorus[8]) would prove constipating. Since facilities for urinary and/or fecal determinations of phosphorus were not available, it would be impossible to determine whether smaller doses would be efficacious.

Venous blood was withdrawn from each patient 3 to 4 hours after breakfast to insure more uniform levels of serum calcium and phosphorus. Initial venipunctures in Groups 1, 2, and 3 were performed between 2 and 14 weeks after medication was started. Second venipunctures were performed approximately 5 weeks later. The initial venipunctures in Group 4 were performed between the twenty-third and thirty-fourth weeks of gestation. Only 9 patients in Group 4 would submit to a second venipuncture; this was performed approximately 3 to 4 weeks later.

It seemed to us that if the leg cramp syndrome were an expression of increased neuromuscular irritability or a "tetanoid-type ailment,"[6] then the muscles should demonstrate increased excitability to galvanic current. Galvanic stimulation (Erb's test) of the peroneal nerve, an accessible motor nerve in the leg, was utilized in an effort to detect latent tetany or increased neuromuscular irritability. A negative Erb's sign or no response to galvanic stimulation indicates normal neuromuscular activity. Thirty patients underwent Erb's test.

Serum calcium was determined by the Clark-Collip[9] modification of the Kramer-Tisdall method; serum phosphorus by the Fiske-Subbarow[10] method, and plasma proteins by the Looney-Walsh[11] method. The value of ionized calcium was calculated by the McLean-Hastings[12] method from the total serum calcium and total plasma proteins.

Results

Group 1.—Ten patients given supplements devoid of calcium, phosphorus, and vitamin D.*

Four out of 10 patients developed leg cramps. Three patients whose leg cramps lasted from one to 9 weeks each drank one to two glasses of milk daily. One patient who experienced severe leg cramps from the fourth to the twenty-seventh week of gestation consumed a grossly inadequate amount of meat and dairy products. This patient demonstrated a negative Erb's sign during the twenty-sixth week. The average values obtained in the blood studies of these 10 patients are shown in Table I.

TABLE I. PATIENTS GIVEN SUPPLEMENTS DEVOID OF CALCIUM, PHOSPHORUS, AND VITAMIN D

	INITIAL VALUE (MG./100 ML.)	AFTER 5-6 WEEKS (MG./100 ML.)	% CHANGE
Total calcium	10.12	9.76	−4
Inorganic phosphorus	3.27	3.82	+17
Total protein	6.66	7.03	+5.5
Calculated ionic calcium	4.65	4.29	−7.7
Ionic calcium/phosphorus	1.53	1.10	−28

Group 2.—Eight patients given supplements containing dicalcium phosphate and vitamin D.†

Two out of 8 patients developed leg cramps from approximately the twenty-seventh week until the twenty-ninth week. The patient with more severe leg cramps exhibited a negative Erb's sign just prior to the onset of and during her 2 week period of leg cramps. Each of these 2 patients with leg cramps consumed four glasses of milk daily in comparison with the six asymptomatic patients who averaged 2.4 glasses of milk daily. The average values obtained in the blood studies of these eight patients are given in Table II.

TABLE II. PATIENTS GIVEN SUPPLEMENTS CONTAINING DICALCIUM PHOSPHATE AND VITAMIN D

	INITIAL VALUE (MG./100 ML.)	AFTER 4-5 WEEKS (MG./100 ML.)	% CHANGE
Total calcium	10.35	9.75	−5.8
Inorganic phosphorus	2.78	3.10	+11.5
Total protein	7.57	6.66	−1.5
Calculated ionic calcium	4.57	4.43	−3.0
Ionic calcium/phosphorus	1.69	1.44	−1.8

Group 3.—Ten patients given supplements containing calcium lactate and vitamin D.‡

Eight out of 10 patients developed leg cramps. Three patients experienced mild cramps lasting no more than 2 weeks. Five patients experienced moderately severe cramps lasting from 3 to 16 weeks. The 2 with the most severe

*Vitamin-mineral capsules without calcium, phosphorus, and vitamin D. No. 7-8239, prepared by Lederle Laboratories.

†Prenatal capsules (Lederle Laboratories).

‡Cyesicaps (Lederle Laboratories).

cases demonstrated a negative Erb's sign. The patient with the most severe cramps drank an insignificant amount of milk but ate an adequate amount of meat and eggs. The average values of the blood studies of these 10 patients are given in Table III.

TABLE III. PATIENTS GIVEN SUPPLEMENTS CONTAINING CALCIUM LACTATE AND VITAMIN D

	INITIAL VALUE (MG./100 ML.)	AFTER 5 WEEKS (MG./100 ML.)	% CHANGE
Total calcium	10.15	10.0	–1.4
Inorganic phosphorus	2.78	3.0	+7.3
Total protein	7.65	6.57	–6.9
Calculated ionic calcium	4.5	4.6	+2.2
Ionic calcium/phosphorus	1.69	1.58	–7.1

Group 4.—Nine patients who complained of leg cramps and received no vitamin-mineral supplements.

The leg cramp syndrome seemed to occur most frequently between the twenty-fourth and thirty-sixth weeks of gestation. The 2 most severe cases lasted from the thirtieth to the thirty-ninth weeks, approximately. Erb's sign was negative in each of the 9 patients with leg cramps. The average daily consumption of milk was two glasses. The average values of the blood studies of these 9 patients are shown in Table IV.

TABLE IV. PATIENTS GIVEN NO VITAMIN-MINERAL SUPPLEMENTS

	INITIAL VALUE (MG./100 ML.)	AFTER 3-4 WEEKS (MG./100 ML.)	% CHANGE
Total calcium	9.7	9.55	–15
Inorganic phosphorus	3.03	3.08	+1.6
Total protein	6.55	6.72	+2.6
Calculated ionic calcium	4.49	4.25	–5.3
Ionic calcium/phosphorus	1.49	1.48	–0.6

Comment

Evaluation of Clinical Studies.—The leg cramp syndrome seems to occur most frequently between the twenty-fourth and thirty-sixth weeks of gestation. There is no apparent correlation between its occurrence and the intake of dairy products.

Two out of 8 patients given dicalcium phosphate developed leg cramps. Eight out of 10 patients given calcium lactate developed leg cramps. Therefore, it appears that calcium lactate is not more efficacious than dicalcium phosphate in preventing and alleviating leg cramps.

Twenty-five patients with leg cramps and 5 patients without leg cramps exhibited negative or normal responses to galvanic stimulation. There were no patients who exhibited positive responses to galvanic stimulation. This seems to indicate that the leg cramp syndrome is not an expression of neuromuscular irritability or latent tetany.

Evaluation of Laboratory Studies.—A slight decrease in total serum calcium was noted in all groups of patients as pregnancy advanced. Our remaining biochemical results did not demonstrate any significant or consistent trends; this may be due to the fact that groups of 10 patients are too small to yield significant results or that significant biochemical results do not occur in the absence of severe metabolic disease. Our biochemical results agreed with those of Cantarow's[13] studies of calcium and phosphorus during pregnancy. We thus failed to duplicate the striking biochemical results of Page and Page and Gross, Wager, and Loving.

Conclusions

Since there has been no agreement on the etiology and management of the leg cramp syndrome during pregnancy, we believe that pregnant women should continue to consume foods rich in calcium and phosphorus despite the presence of leg cramps. The Food and Nutrition Board[14] of the National Research Council has recommended a daily intake of 1.5 Gm. of calcium and of phosphorus during the third trimester of pregnancy.

Whitacre[15] endorsed the simplified Canadian nutrition guide that recommends the consumption of 1.5 pints of milk and one serving of meat daily, and eggs and cheese three times weekly during the second half of pregnancy. Vitamin-mineral supplements are valuable if the intake of any of the recommended foods is reduced. Unless the pregnant woman complains of heartburn and/or diarrhea, the addition of aluminum hydroxide gel to the diet is superfluous.

Summary

1. The leg cramp syndrome seems to occur most frequently between the twenty-fourth and thirty-sixth weeks of gestation.

2. The pregnant woman who experiences leg cramps does not demonstrate increased neuromuscular irritability as evidenced by a negative Erb's sign.

3. No evidence was found to support the contention that increased ingestion of dairy products predisposed to the occurrence of leg cramps.

4. Calcium lactate was found to be no more efficacious than dicalcium phosphate in the prevention and alleviation of leg cramps.

5. The pregnant woman should be encouraged to consume the minimum daily amounts of the essential vitamins and minerals in the form of natural foods recommended by the National Research Council or the Canadian Council on Nutrition, supplemented with vitamin-mineral capsules or tablets when deemed necessary. The presence of leg cramps should not interfere with a well-balanced dietary intake.

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References

1. Page, E. W., and Page, E. P.: Obst. & Gynec. **1**: 94, 1953.
2. Robinson, Margaret: J. Obst. & Gynaec. Brit. Emp. **54**: 826, 1947.
3. Fandrich, T. S.: J. Michigan M. Soc. **53**: 862, 1954.
4. Wolff, J. R.: Illinois M. J. **105**: 6, 1954.
5. Hawker, W. D.: Missouri Med. **51**: 727, 1954.
6. Gross, M., Wager, H. P., and Loving, M.: Bull. Margaret Hague Maternity Hosp. **6**: 107, 1953.
7. Hardy, J. A.: Obst. & Gynec. **8**: 565, 1956.

8. Shorr, E., and Carter, A. C.: J. A. M. A. **144**: 1549, 1950.
9. Clark, E. P., and Collip, J. B.: J. Biol. Chem **63**: 461, 1925.
10. Fiske, C. H., and Subbarow, Y.: J. Biol. Chem. **66**: 375, 1925.
11. Looney, J. M., and Walsh, A. I.: J. Biol. Chem. **130**: 635, 1939.
12. McLean, F. C., and Hastings, A. B.: Am. J. M. Sc. **189**: 601, 1935.
13. Cantarow, A., and Trumper, M.: Clinical Biochemistry, Philadelphia, 1940, W. B. Saunders Company.
14. Eastman, N. J.: Williams Obstetrics, New York, 1950, Appleton-Century-Crofts, Inc., p. 314.
15. Whitacre, F. E.: J. A. M. A. **155**: 112, 1954.

PREGNANCY AND LEPROSY

A Review of 52 Pregnancies in 26 Patients With Leprosy

JOHN A. KING, M.D., AND ROBERT A. MARKS, M.D.,
NEW ORLEANS, LA.

(From the Department of Obstetrics and Gynecology, United States Public Health Service Hospital, New Orleans, and the United States Public Health Service Hospital, Carville, Louisiana)

MEDICAL literature in the English language contains few references to the association of leprosy and pregnancy. Standard texts[1, 2] mention that the two can occur concurrently, and that leprosy usually exerts no effect on the pregnancy. In view of the paucity of references on this subject it was felt that a review of the records of the National Leprosarium (U. S. Public Health Service Hospital) at Carville, Louisiana, and the U. S. Public Health Service Hospital in New Orleans would be valuable in ascertaining the courses of the two conditions when concurrent.

Leprosy may be defined as an extremely chronic, slowly progressive, systemic granulomatous disease, presumably due to *Mycobacterium leprae,* which involves the skin, peripheral nerves, and viscera.[3] Complications in the form of skin ulceration, bone absorption, deformities of the extremities, ocular and nasal involvement, testicular atrophy, laryngeal obstruction, and amyloidosis may occur. Spontaneous regression to the point of arrest rarely occurs; apparent arrest with treatment other than the sulfones has been relatively rare. Endemic foci in the United States of America exist in Louisiana, Florida, Texas, and California.

The literature shows the incidence of the disease in the female to be lower than in the male, with the ratio being about 60 to 40.[4] In many cases, infection becomes evident or is diagnosed during childhood or puberty,[2, 4] children apparently being much more susceptible to infection than adults. Involvement of the genital organs is extremely rare in the female, but involvement of the testicles with resultant sterility is frequent in lepromatous leprosy.[5]

Most leprologists feel that prolonged and intimate contact with a person who presents lesions discharging *Myco. leprae* is usually necessary for infection of a second party. Conjugal infection is rare (4 per cent), however, and it is unusual for nurses, physicians, or others working with known cases to acquire the disease. Some patients can give no definite history of contact. The incubation period may be extremely variable, many years, as in the case of war veterans,[6] who have presumably had no contact with leprosy since serving in endemic areas, or fairly short, as in the case of children.

According to Simmons,[2] children born to a mother who has leprosy, if separated from the mother at birth and reared by healthy foster parents, will acquire the disease no more frequently than children born to a normal mother, but there is an incidence of 25 per cent of leprosy in such children if brought up by affected parents. Racial immunity varies, those of Northern European stock apparently having much higher immunity to leprosy, but in a study of patients at Carville, Hopkins[7] found proportionately more white than Negro patients involved in cases of Louisiana origin.

It has been stated by Ryrie[8] that the disease has no effect on pregnancy, while the pregnancy exerts a profound effect on the course of the leprosy. This he attributes to mineral depletion and metabolic changes in the woman during pregnancy. This statement is often repeated in the literature.[2, 9] It has also been noted that acid-fast bacilli are found rarely in placentas and cords.[10, 11, 12] This may or may not be *Myco. leprae,* and may or may not represent actual infection.

de Souza-Araujo[13] stated that pregnancy and delivery are frequent factors in the development or aggravation of leprosy, and that the absence of aggravation under the influence of pregnancy or labor indicates that leprosy is cured. This was also noted by Tajiri[9]—48 cases of aggravation in 100 pregnancies.

Of interest is the common finding of a false positive serologic test for syphilis in patients with leprosy.[14] Many of these patients give a history of antisyphilis therapy before their skin lesions are correctly diagnosed.

Material

The histories and charts of 26 women with active lepromatous leprosy, who were patients at the two hospitals mentioned, were reviewed. There were 52 pregnancies from which the data were acquired.

Results

Prior to the common use of the sulfones starting in 1946 the mainstay of treatment was chaulmoogra oil in addition to general supportive measures. The treatment prior to the sulfones is classified as "other treatment" for the sake of simplicity.

Of the 26 cases reviewed in this series it was found that leprosy presumably started near the menarche in 5 and at the time of or shortly after pregnancy in 9 cases (Table I). There was no definite relationship between the onset of leprosy and the menarche or pregnancy in 11 patients. The history of the onset was not adequate in one patient of the 26 studied. Of course, it is difficult to say exactly when leprosy begins because of the frequently insidious onset and delay in diagnosis and chronicity of lesions.

TABLE I. TIME OF ONSET OF LEPROSY

At time of or shortly after menarche	5
During or shortly after a pregnancy	9
No relationship to menarche or pregnancy	11
History unobtainable	1
Total no. of patients	26

In Table II it can be seen that during the course of 23 pregnancies when no treatment was given to combat the leprosy, the disease was apparently aggravated in 18 cases and not aggravated in 5 cases. There were no cases in which improvement was evident during pregnancy.

TABLE II. ANALYSIS OF EFFECT OF PREGNANCY BY TREATMENT OF LEPROSY

LEPROSY	NO. OF PREGNANCIES
Untreated.—	
Aggravated	18
Not aggravated	5
Improved	0
Total	23
Sulfone-Treated.—	
Aggravated	5
Not aggravated	17
Improved	1
Total	23
Other Methods of Treatment.—	
Aggravated	1
Not aggravated	5
Improved	0
Total	6

In Table II 23 other pregnancies are summarized. The disease was apparently aggravated in 5 instances, unchanged in 17, and improved in one case. These patients were all treated during their pregnancies with drugs of the sulfone group.

The patients who received other methods of treatment are also shown in Table II. As previously noted, these are mostly cases handled before 1946. Aggravation of the leprosy was noted in one case, there was no change in 5, and improvement in none, a total of 6 cases.

The following case reports illustrate fairly typical courses:

CASE 10.—M. L. was a 22-year-old gravida i, para i, when admitted to Carville in 1939 with a diagnosis of lepromatous leprosy. This diagnosis had been made from biopsy of a chronic raised, papular, red rash which had become widespread during a recent pregnancy. She was treated with chaulmoogra oil, and later in 1939 she became pregnant again. During this pregnancy there was edema of the extremities and face, and paresthesias of the hands were noted. The pregnancy was otherwise uneventful, and the delivery was spontaneous. With the advent of the sulfones in 1946, she was started on glucosulfone sodium (Promin*). Just prior to this treatment she had once again become pregnant, and during the pregnancy there was progression of the skin lesions and anesthetic areas of the feet, hands, and trunk, even though she received continuous therapy. She had an uneventful delivery of twins, and following this developed generalized amyloidosis, with nephrosis and hypertension. She died 6 years later of renal failure, and autopsy showed extensive amyloidosis, even in the ovarian arteries. Skin examinations for *Myco. leprae* remained positive throughout the patient's course.

CASE 37.—J. B. was admitted to Carville in 1944 at the age of 14 years. The diagnosis of lepromatous leprosy had been made by biopsy of lesions which had been present for 5 years. These were irregular, anesthetic, brown macules on the trunk, and small nodules on the ears and cheeks and extensor surfaces of the limbs. She received Promin therapy, but deserted in 1947. She had an apparently normal pregnancy and delivery in 1948, without any apparent progression of the disease. She returned to Carville early in 1949, in the early weeks of her second pregnancy, and at that time exhibited maculopapular lesions over the trunk and definite nodules on the face, arms, and legs, with edema of the feet and legs. She again received Promin treatment, and before the end of the pregnancy had shown definite improvement in the skin lesions. At term, after a labor of 4½ hours, she was delivered of a boy weighing 6 pounds, 5 ounces, by low forceps under saddle block anesthesia. There was no episiotomy or laceration.

*Parke, Davis & Company, Detroit, Mich.

CASE 16.—G. G., a 24-year-old gravida ii, para ii, white woman, was admitted to the leprosarium in 1948 with a history of having noted pigmented macular and red papular skin lesions during her first pregnancy in 1942. There were no further lesions until 1947, during the second pregnancy, when more pigmented macules and red papules and nodular lesions appeared on the trunk, extremities, and face. Following the second pregnancy, a diagnosis of lepromatous leprosy was made by skin biopsy. She was treated with acetosulfone (Promacetin*) and definite improvement in the skin lesions was noted. In 1949 the improvement continued during 2 months of her third pregnancy until its termination by spontaneous abortion. A vaginal hysterectomy was done in 1951 for intractable menorrhagia and uterine prolapse. The removed tissues showed no evidence of acid-fast bacilli. She is still improving under sulfone therapy.

CASE 49.—E. M. was a 17-year-old gravida i, para i, when admitted to Carville in 1931 with a history of a pink macular rash on the face, limbs, and body. She also had several nonpigmented nodules on the arms and legs. These lesions had appeared immediately after her apparently normal pregnancy and delivery 4 months previously. A diagnosis of lepromatous leprosy was made from a skin biopsy, and she was treated with chaulmoogra oil and supportive therapy from the time of her admission. The lesions remained stable during a second pregnancy in 1937, but she showed some albuminuria and hypertension on the basis of her previously diagnosed renal amyloidosis. She had a normal spontaneous delivery of a female child, and her postpartum course was uneventful. In 1945 Promin therapy was started, and there was improvement in the skin lesions, but steady advancement of renal insufficiency was noted. In 1949 she again became pregnant, and throughout this pregnancy she was very ill with a refractory anemia and marked elevation of the nonprotein nitrogen. Toward the seventh month it was doubtful that she would survive. She went into labor spontaneously, however, and after 14 hours was delivered under spinal anesthesia by low forceps of premature twins weighing 4 pounds, 3 ounces, and 3 pounds, 4 ounces. Both babies did well following delivery, and the mother recuperated rapidly. Nevertheless, her renal function has remained poor even though the skin lesions have improved markedly.

Her second child, who had visited her twice monthly since the age of 9, was found to have leprosy at the age of 15. She was admitted to the leprosarium in 1952.

In general, labors and deliveries were conducted as in other obstetric cases, and spinal or general anesthetics were given without untoward effect. In this series there were no cesarean sections. The postpartum courses were uneventful except for one case of postpartum hemorrhage which eventually required total hysterectomy for control. Of interest is the number of twin pregnancies which has occurred, there being 6 sets of twins in the 52 pregnancies. This is approximately ten times the usual incidence of twins. In 6 cases in which microscopic examination of the placenta was recorded, neither acid-fast bacilli nor other evidence of placental involvement was noted.

The following procedure is in use at the present time with regard to the separation of the child from the infected mother. The mother is not allowed to nurse or handle the child while she is in the hospital; if the family of the mother or father is able to care for the child and is willing to do so, he is allowed to go to them. He is then checked at intervals for evidence of infection by the local health agency.

If no member of the family of either parent can accept custody of the child, he is cared for by a social agency—either placed in a foster home or adoption is arranged if the parents consent. Only one child is known to have developed leprosy (Case 49, above) and, as noted, she had contact with her mother during childhood.

*Parke, Davis & Company, Detroit, Mich.

Conclusions

Leprosy is of interest to physicians practicing in endemic areas, and it is important that obstetricians and gynecologists be aware of the effect of pregnancy on the disease. The fairly common onset at puberty, during or shortly after a pregnancy, and aggravation during pregnancy should be borne in mind. In the endemic areas, if an obstetric patient should present herself with chronic skin lesions and a positive serologic test, for syphilis, especially if there is any loss of sensation in the lesions, she should be thoroughly investigated for the possibility of leprosy.

Of interest are the facts that the child born to an affected individual is not infected at birth, and, if reared in a healthy environment, is no more likely to contract the disease than other children residing in the community; and that the disease, even when active, seems to have no effect on the course of the pregnancy. The efficacy of the sulfone group of drugs in preventing aggravation of leprosy during pregnancy is well illustrated in the present study.

Summary

1. Fifty-two pregnancies in 26 women with active lepromatous leprosy are reviewed.

2. The onset of leprosy apparently occurred during or shortly after the menarche or pregnancy in 14 patients.

3. Aggravation of the disease occurred in 18 of 23 pregnancies during which the leprosy was not treated.

4. Aggravation occurred in only 5 of 23 pregnancies during which the patients were treated with one of the sulfone drugs.

5. Of 6 pregnancies in patients who received other forms of treatment for leprosy, the disease was aggravated in one instance.

6. Two cases of amyloidosis with renal insufficiency, one case of preeclampsia, one case of severe postpartum hemorrhage, and 6 twin pregnancies were noted.

References

1. Eastman, N. J.: William's Obstetrics, ed. 10, New York, 1952, Appleton-Century-Crofts, Inc.
2. Simmons, J. S.: In Oxford Med. **5:** 387, Pt. 1, 1949.
3. Powell, C. S., and Swan, L. L.: Am. J. Path. **31:** 1131, 1955.
4. Romero, A., and Brenes Ibarra, A. A.: Rev. méd. Costa Rica **8:** 294, 1948.
5. Grabstald, H., and Swan, L. L.: J. A. M. A. **149:** 1287, 1952.
6. Aycock, W. L., and Gordon, J. E.: Am. J. M. Sc. **214:** 329, 1947.
7. Hopkins, R.: In Tuberculosis and Leprosy—The Mycobacterial Diseases, Am. Assoc. Adv. Sc., Lancaster, Pa., 1938, Science Press Printing Company, vol. 1, p. 112.
8. Ryrie, G. A.: Brit. M. J. **2:** 39, 1938.
9. Tajirí, I.: Internat. J. Leprosy **4:** 189, 1936.
10. Cerruti, H., and Bechelli, L. M.: Rev. brasil leprol. **4:** 199, 1936. (Abstracted in Internat. J. Leprosy **6:** 583, 1936.)
11. Vigne, P., and Guerin-Valmale: Bull. Soc. d'obst. et de gynéc. **23:** 75, 1934.
12. Inaba, T.: LaLepro 9, Supp. III, 1938. (Abstract) Author's summary in Internat. J. Leprosy **8:** 394, 1940.
13. de Souza-Araujo, H. C.: Internat. J. Leprosy **5:** 117, 1937. (Abstract.)
14. Cecil, R. L.: Textbook of Medicine, ed. 6, New York, 1943, W. B. Saunders Company.

DEPARTMENT OF CURRENT OPINION

Re-evaluation

THE REPUDIATION OF LOW-DOSAGE IRRADIATION OF THE OVARIES

S. LEON ISRAEL, M.D., PHILADELPHIA, PA.

(From the Department of Gynecology-Obstetrics, Graduate School of Medicine, University of Pennsylvania)

LOW-DOSAGE irradiation of the pituitary gland and ovaries for the correction of abnormalities of menstrual rhythm and anovulatory sterility, an effective and economical form of therapy, albeit an empiric one, may no longer be used.

Few denied the clinical effectiveness of low-dosage irradiation in properly selected amenorrheal patients. Nor did anyone report adverse effects on the patient and her immediate offspring. There was nonetheless a reluctance on the part of many physicians to employ such irradiation of the ovaries because of the possibility of long-term genetic effects, unobtrusive mutations of the germ plasm which would not become evident until many generations hence. This genetic argument, a stumbling block to the widespread use of low-dosage irradiation, was either hurdled briskly or brushed aside gently by sincere enthusiasts including the present writer.[1-5] Their reports give the clinical details of low-dosage therapy, including the minutiae of its technique, hypothetical explanations of its empiric action, the proper selection of patient-candidates for it, and statistics of its more than satisfactory results in secondary amenorrhea and anovulatory sterility. The variegated rationalizations of these proponents took the form of counterarguments to the views advanced by geneticists (Table I). We live, however, in a rapidly changing world, the supercharged atomic atmosphere of which makes adaptation to change imperative.

TABLE I. CLINICAL ARGUMENTS FOR AND GENETIC REPLIES AGAINST LOW-DOSAGE IRRADIATION OF THE OVARIES

CLINICAL[1-5]	GENETIC[8-15]
1. The quantity of x-rays employed to study genetic effects of irradiation in plants and animals is many times that used in low-dosage irradiation therapy. The low dosage employed in therapy of the gonads is too small to alter genes.	1. There is no threshold dose of gonadal irradiation below which mutations are not produced. As far as genetic effects are concerned, the only safe dose of high-energy radiation is *no* radiation.
2. Whole-body irradiation, imposed by the small size of some experimental animals, sets off a complicated sequence of effects. It is not possible to compare with accuracy the effects of whole-body irradiation, as pertains in fruit fly or mouse, with those following irradiation of specific organ areas.	2. The somatic effects of whole-body irradiation and the fact that man is neither an overgrown fruit fly nor a large mouse are granted. But the alteration of the "chemically coded" hereditary material occurs irrespective of the other effects of whole-body irradiation. Maize or mouse, fruit fly or man, genes are genes.
3. The mutations created by irradiation of the gonads are the same as those which tend to develop spontaneously; they merely occur at an increased rate. All are not harmful, some are beneficial. Most of the deleterious ones, whether spontaneous or induced, are eliminated with time.	3. Most new mutations are more or less deleterious. Less than 1 in 100—probably less than 1 in 1,000—is advantageous. An increased frequency of mutations, as induced by high-energy radiation, causes a preponderance of harmful ones.
4. The mutant gene is recessive. It will not be harmful unless it is paired by marriage with a similarly altered gene. Since very few women are subjected to low-dosage ovarian irradiation, there is little possibility that progeny of gonad-irradiated lines will intermarry. The danger to future generations is thus automatically minimized by the population-dilution factor.	4. This is a common misconception. Although recessive harmful mutations do not produce their maximum danger except when inherited in a double dose, the efficiency of a single normal gene is rarely fully equal to that of two. There is some slight damage to the bearer, to the first generation, and to all subsequent progeny from any deleterious mutation, even if heterozygous. "A genetic death does not always produce a cadaver."[14]
5. Clinicians have pointed to the physical beauty and good health of second- and third-generation offspring of irradiated women to support their thesis. In fact, there were no obvious deformities of the children born to women who survived the atomic explosions at Hiroshima and Nagasaki.	5. Genetic changes would not be apparent in third-generation family photographs. Such sublethal effects may not be evident in progeny until 3 times 3 generations later. Mutational changes so great as to damage the first generation are "invisible" because they result in abortion or stillbirth "of unknown origin."

Irradiation of the Gonads

The summary reports of the United States National Academy of Sciences[6] and of the Medical Research Council of Great Britain[7] on the hazards of nuclear and allied radiations to man were released simultaneously during June, 1956. Both documents emphasize the importance of reducing the medical usage of ionizing radiation to an absolute minimum, in spite of the fact that the quantity of radiation received by each person on earth from his environmental background and exposure to fallout varies widely.[8] The anxiety expressed in both reports revolves about the subject of possible damage to the genes during the first 30 years of life, a period demarcated as the one most important to reproduction. Each manifesto recommends an upper limit to total exposure of the gonads during those years of 50 r. Although there are some minor differences between the two publications in the manner of expressing permissible radiation dosage for the general population, the warning

inherent in each is unmistakable. Even though both reports stress also the gaps in the present knowledge of human genetics, these areas of ignorance being recognized by geneticists themselves,[10-14] both also agree on the threatening role played by the therapeutic use of x-rays.

"Few more fateful documents," wrote Glass,[15] "have been submitted to the consideration of the modern world than these two reports. They in no way claim finality. Yet what they say is of such urgency and such far-reaching significance that every tool of public education and legislative power needs to be fully employed in promoting a wider appreciation of the foreseeable hazards, not alone of nuclear war, but equally of the expansion of peaceful uses of atomic energy. It is shocking to realize that already virtually half of the maximum reasonable allowance of exposure for the whole population is pre-empted by medical and dental diagnostic and therapeutic uses of ionizing radiation. We must henceforth guard jealously every expenditure of this radiation allowance. The cost of negligence would be genetic bankruptcy, and from that bankruptcy there might be no recovery, for nation or for mankind."

Irradiation of the Pituitary

Low-dosage irradiation to the pituitary alone, seemingly indicated in the obese patient whose amenorrhea is attributed to hypopituitarism, is of dubious value but can do no harm. The probable dose to the gonads from such x-ray therapy is similar to that of dental x-rays, estimated at 0.1 roentgen.[9] Kaplan[16] expressed doubt concerning the ability of such irradiation to effect hormone changes in the pituitary. Moreover, the comparative endocrine studies of Rakoff[17] before and after low-dosage irradiation of the pituitary alone, of the ovaries alone, and of the pituitary and ovaries in women with long-standing problems of anovulation failed to demonstrate any benefit from treatment of the pituitary alone. In fact, Rakoff's data suggest that the salutary results of irradiation of the pituitary and ovaries stem only from the response of the ovaries. On the other hand, Farris[18] regards low-dosage irradiation of the pituitary alone as a valuable form of treatment in sterility caused by anovulation. I can see no objection to its use.

Conclusion

When serious-minded scientists of the atomic age issue universal recommendations aimed at decreasing the hazards of ionizing radiation to future generations of mankind, we cannot help but be persuaded morally to discontinue low-dosage irradiation of the gonads. We must do this even if the hazards are theoretical and are minimized by the fact that such therapy is applied to but few women of the world's population. We are bound ethically by the simple clarity of these words of Neel[19]: "The greatest asset of mankind today is its germ plasm—whatsoever threatens this must be viewed with concern."

References

1. Drips, D. G.: Am. J. Obst. & Gynec. **57**: 789, 1948.
2. Kaplan, I. I.: Am. J. Obst. & Gynec. **57**: 622, 1949.
3. Mazer, C., and Israel, S. L.: Diagnosis and Treatment of Menstrual Disorders and Sterility, ed. 3, New York, 1951, Paul B. Hoeber, Inc.
4. Israel, S. L.: Am. J. Obst. & Gynec. **64**: 971, 1952.
5. Fullenlove, T. M., Haman, J. O., and Williams, A. J.: Fertil. & Steril. **7**: 18, 1956.
6. United States National Academy of Sciences: Biological Effects of Radiation, Science **123**: 1157, 1956.

7. Medical Research Council of Great Britain: Hazards to Man of Nuclear and Allied Radiations, London, 1956, Her Majesty's Stationery Office.
8. Muller, H. J.: Am. J. Obst. & Gynec. **67**: 467, 1954.
9. Glass, B.: Science **126**: 241, 1957.
10. Dunn, L. C.: Scient. Month. **84**: 6, 1957.
11. Evans, R. D.: Science **109**: 299, 1949.
12. Ingram, M.: Science **111**: 103, 1950.
13. Keosian, J.: Science **122**: 586, 1955.
14. Dobzhansky, T.: Science **126**: 191, 1957.
15. Glass, B.: J. Hered. **47**: 260, 1956.
16. Kaplan, I. I.: Am. J. Roentgenol. **59**: 370, 1948.
17. Rakoff, A. E.: J. Clin. Endocrinol. **16**: 969, 1956.
18. Farris, E. J.: Human Ovulation and Fertility, Philadelphia, 1956, J. B. Lippincott Company.
19. Neel, J. V.: J. M. Educ. **32**: 493, 1957.

2116 Spruce Street
Philadelphia 3, Pennsylvania

THE TREATMENT OF FEMALE STERILITY WITH X-RAY THERAPY DIRECTED TO THE PITUITARY AND OVARIES

IRA I. KAPLAN, M.D., NEW YORK, N. Y.

IN 1928 I[1] published my first report on the x-ray treatment of women for amenorrhea and sterility in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY. This covered observation of only 38 women treated over a period of 3 years. The present paper reappraises the stand I took at that time and brings three decades of material up to date. It is based on my treatment of over 700 married women, referred for infertility in the years since 1924.

The influence of x-ray irradiation on the life of human beings has recently been discussed with increasing intensity, and there has been a good deal of disagreement between the geneticists and clinicians, especially in reference to the possible genetic effects of x-ray on the progeny of irradiated females.

The method employed has remained quite constant. A tissue dose of 90 r (with back scatter) was administered to the pituitary and 60 to 65 r to each ovary (with back scatter), with the following factors: 200 kv., 1 mm. copper half-value layer. Treatment was given three times at intervals of 7 days.

Technique.—The technique of treatment is as follows: At the first session 50 r is administered to the anterior right and left pelvic areas, with the rays directed through the ovaries, and at the same session 75 r is directed to the pituitary through a central forehead portal (r dose measured in air). Seven days later 75 r is administered to the right and left posterior pelvic fields, with the rays directed through the ovaries, and 75 r through the center forehead to the pituitary. Seven days later treatment similar to that of the first day is administered to the anterior pelvis and the pituitary.

Pertinent Data on Treated Patients.—The age of the patients treated ranged from 18 to 42 years.

In most cases irregular menstruation was associated with the sterility in the group of women who responded to irradiation. In 64, menstruation was regular, in 235 irregular, and in 42 cases menstruation was at first regular, then became irregular. The irregularity varied, with periods occurring every 2 or 3 months, once or twice a year, or none for years.

The period of sterility before treatment extended from 1 to 19 years. In many instances it was known from the time of the menarche that a problem of infertility would present itself, since in almost all cases there was an early history of irregularity. Table I indicates the years of sterility, counting from the age at marriage to the age when x-ray therapy was administered. In 5 cases there was a second marriage and the sterility is reckoned from the age at the second marriage.

In 60 cases the patient had previously conceived, borne a child (21), or miscarried (39), and then failed to conceive again until irradiation was administered.

TABLE I. LENGTH OF STERILITY IN 341 PATIENTS WHO RESPONDED

PERIOD OF STERILITY	NO. OF PATIENTS
1 year	23
2 years	45
3 years	67
4 years	49
5 years	40
6 years	39
7 years	21
8 years	13
9 years	18
10 years	6
11 years	5
12 years	5
13 years	5
14 years	1
15 years	2
19 years	1
Not recorded	1
Total	341

Results.—A report of the clinical results in 636 treated cases is given in Table II.

TABLE II. CLINICAL RESULTS

CLASSIFICATION OF PATIENTS		NO.	
Total registered, 1924-1957		816	
Not treated, or treatment not completed because of: (1) anatomical pathology, (2) closed Fallopian tubes, or (3) failure to return			20
Lost track of			157
Failed to conceive			249
Husband proved impotent	5		
Adopted children, but failed subsequently to conceive and bear children	44		
Conceived following irradiation			341
Conceptions following irradiation	660		
Bore living children	308		
Conceived but miscarried	84		
No. of these who conceived again and successfully bore children	61		
Conceived but had ectopic pregnancies	7		
Children born following irradiation		540	

It is currently known that the average incidence of miscarriage in the United States is 10 per cent. In my series 84 women who conceived following irradiation miscarried (some several times), and 61 conceived again without further difficulty and bore normal children.

Just why miscariage should follow irradiation in some cases and not in others is not definitely known. It has been suggested[2] that conception following too close upon the irradiation might be inducive to miscarriage.

TABLE III. BIRTH DISTRIBUTION OF 308 WOMEN WHO BORE CHILDREN

NO. OF WOMEN	NO. OF CHILDREN
140	1 child
115	2 children
42	3 children
11	4 children
Total 308	

As a rule, once the patient responded and conceived and bore a child she continued to function normally and, if she wished, was able to conceive again, and bear children. In 140 cases the woman conceived and bore one child, in 168 cases the women bore more than one child. Table III illustrates the birth distribution of the 308 women who bore children following irradiation.

In some instances, when a woman failed to respond within 6 to 8 months following x-ray therapy, a second treatment was advised. Twenty-two patients were treated twice and 11 responded, conceived, and bore children. In 2 cases a single treatment or booster was given 6 to 8 weeks after the third treatment of the regular series had been administered, with response.

Corner[3] says, there is "a widespread popular belief shared by many physicians, that a woman who adopts a baby, despairing of her own fertility, is likely to become pregnant soon afterward." He quotes John Rock as having marshaled statistical data indicating the fallacy of this belief. Forty-four women in my series, who failed to respond to x-ray therapy, are known to have adopted a child but have not subsequently borne children.

Table IV illustrates statistically the number of F 1 (first generation children born to irradiated mothers.

TABLE IV. F 1 CHILDREN BORN FOLLOWING IRRADIATION

Children born following irradiation		540
Boys	265	
Girls	275	
These include 5 sets of twins		
F 1 children born alive		523
Normal living F 1 children	520	
Living F 1 children with abnormalities	3	
F 1 children who died or were born dead (see Table V for details)		17

Abnormalities Following Irradiation

One of the important questions is that of the occurrence of abnormalities following irradiation.

Abnormalities are found in newborn children in cases where no x-rays have been administered. McIntosh[4] and his co-workers reported a 7 per cent incidence of abnormal children born in a 5 year study of 5,965 pregnancies at the Babies Hospital and the Sloane Hospital for Women.

Jacobziner[5] and his co-workers state that congenital malformations constitute an important segment of the over-all problem of fetal wastage, a major health problem.

Davis and Potter[6] state there are many factors implicated in the cause of human malformation. They quote the 1950 report of the National Bureau of Vital Statistics showing a neonatal mortality from malformations of 4.4 per 1,000 births of the normal population. In a study of 5,000 consecutive births at the Chicago Lying-in Hospital in 1951-1952 about 4.2 per 1,000 showed malformations. They conclude from their observations that genetic disturbances can rarely be shown to be the cause of lethal malformations.

In my series there are only 3 living F 1 children who were born with abnormalities following irradiation of their sterile mothers. Two of these women previously bore a normal child and then bore a second one with a physical abnormality, and the other, one with mental retardation. The third has not yet borne a second child.

The details of these cases are as follows:

Mrs. G. C., irradiated Feb. 26, 1952, bore a boy baby; the second child, born on Nov. 17, 1955, had only one finger on one hand and four toes on one foot.

Mrs. E. K., irradiated Sept. 1, 1950, bore a boy baby; the second son, born on Aug. 21, 1954, had slight mental retardation and premature closure of the fontanelles.

Mrs. E. B., irradiated Sept. 14, 1951, bore a girl baby on May 6, 1957, who has 6 digits (an extra thumb on one hand).

Stillbirth and Irradiation

The question of the relationship of irradiation to the incidence of stillbirth is still not definitely determined.

Neel and Schull[7] stated that the normal rate of stillbirths in 1950 in Michigan was 1.9 per cent and this is little different from what they found in Hiroshima (1.27 per cent) and Nagasaki (1.31 per cent) following irradiation from the atomic bombing. They say that there is no clearly consistent relationship between maternal exposure and the stillbirth rate.

In the 1945 Summary of Vital Statistics the 1943 stillbirth rate is given as 26.7 per cent of all live births in the general population.

In my series of 540 children born following irradiation, 14 of the F 1 children were born dead or died shortly after birth, a percentage of 2.6 over a period of 32 years.

Two older children died, one at 6 years of tetanus and the other at 2 was accidentally drowned. One other child died at age 3 from Tay-Sachs disease. In the ancestry of this child there is a history of amaurotic familial idiocy. Table V gives the details of the F 1 children who died.

TABLE V. DETAILS OF DEATHS OF F 1 CHILDREN

Probably Genetic Deaths.—

Mrs. E. A.—Boy, born April 14, 1954; died 15 minutes after birth. Hydrocephalus. Second child of this mother normal

Mrs. S. H.—Boy, born April, 1954; died following surgery at 5 weeks of age, Hirschsprung's disease. Subsequent, normal girl born Dec. 30, 1955

Mrs. L. M.—Girl, born Nov. 1, 1930; died at birth, hydrocephalus (this may have been due to irradiation of the fetus in utero, reported by me in 1932[8]). Mother subsequently bore two normal girls

Mrs. R. S.—Girl, born April 3, 1952; died 3 years after birth of Tay-Sachs disease. Familial amaurotic idiocy in both parents' families

Possibly Genetic Deaths.—

Mrs. J. C.—Premature stillbirth in 1944

Mrs. A. K.—Nov. 3, 1949, premature stillbirth at 6 months

Mrs. H. P.—Premature 8 month boy in February, 1956

Mrs. L. J.—Girl born October, 1955; died 4 days after birth of pneumonia

Mrs. M. S.—Treated July, 1951, pregnant October, 1951, in auto accident, December, 1951; premature birth of girl who died the next day

Nongenetic Deaths.—

Mrs. B. A.—Stillborn girl Jan. 10, 1949. Cord strangulation

Mrs. S. B.—Stillborn boy March 9, 1949. Cord strangulation

Mrs. L. J.—Stillborn boy June, 1943. Cord strangulation

Mrs. F. T.—Boy born alive at full term July 20, 1942, weight 1 pound, 14 ounces; died in 3 days. First child of this mother normal. Hysterectomy followed birth of second child. Uterus almost completely filled by very large fibroid. Evidently this growth had inhibited proper fetal development

Accidental Nongenetic Deaths.—

Mrs. G. G.—Boy born July 3, 1947; died at age 2 from accidental drowning in pond

Mrs. B. E.—Boy born April 4, 1928; died at age 6 of tetanus

Cancer and Irradiation

Another important question is that of the influence of irradiation on the development of cancer in children born to women exposed to x-rays.

In 1956, Steward,[9] studying the reported cases of leukemia in children in England, over a given period, found that often the mother had received pelvic irradiation prior to giving birth. In all but 2 instances the x-rays were administered to a pregnant woman, with a fetus already present in utero. These cases obviously differ from my cases in which there was therapeutic irradiation to a nonpregnant woman for the treatment of sterility.

Recently De Vore and his co-workers[10] have reported that their investigation of the Hodgkins' syndrome showed that there is a familial incidence in the occurrence of multiple lymphomas of large extent, and this extensive occurrence had no relationship to exposure to irradiation.

Although irradiation for sterility entailed the direct administration of x-ray to the ovaries, no child in my series of 540 children and 43 grandchildren has shown any evidence of having developed any malignancy, even children who have now passed 25 or 30 years of life, quite past the usual age period for the occurrence of childhood cancer. Brues[11] says one of the most frequently asked questions is, "how much irradiation is safe?"

Since Muller's[12] report on the effect of x-rays on mutation in Drosophila, many assumptions have been made referring to genetic effects due to x-ray therapy on the human race. The geneticists believe any dose is deleterious and Russell[13] states that there is no threshold dose of x-ray. Slatis[14] says that were man to be poisoned by irradiation so that his mutation rate were doubled, it would be several generations before the accumulation of new mutations would amount to much. It seems unlikely that doubling the mutation rate would pose a serious problem to the life of the species, and it would go almost unnoticed.

Recently Neel,[15] after a careful analysis of the findings in some 65,431 infants whose parents were exposed to the atomic bombing at Hiroshima and Nagasaki, reported that the investigators were unable to demonstrate any clear-cut differences between the children of irradiated and of control parents.

Adverse conclusions by geneticists are based on observations made solely on the basis of animal experimentation, and human experience has evidently not been analogous.

One of the geneticist's insistent pronouncements is that irradiation of the gonads of women who subsequently become pregnant would produce deleterious effects on their progeny. Rubin[16] states that while the mature follicles of the human ovary may be adversely affected by irradiation, the primordial ova are quite insensitive to x-rays, and go on to maturity, fertilization, and the production of normal progeny.

Grandchildren of Women Irradiated for Sterility

Human abnormalities from irradiation of women who subsequently bear children should be, it is averred, observable in their F 2 (second generation) progeny. The most important observation in all this study is that which concerns the grandchildren of these irradiated women. A further proof of the absence of transmitted genetic abnormality following irradiation is the birth of 43 normal F 2 children to the married children of the originally irradiated mothers.

The first daughter of an irradiated mother to marry was born in January, 1927, to a woman treated in June, 1925. She was married in March, 1946, and is now the mother of 2 children, a boy born on Oct. 22, 1948, and a girl born on Oct. 13, 1950. Both are normal.

Since then, 34 F 1 children, 14 males and 20 females, have married, and one female is now engaged. From these marriages there have already been

born 43 normal F 2 children, that is, grandchildren of the originally irradiated infertile women. At present there are 3 more grandchildren on the way to being born. In the group of living F 2 children there are 22 boys and 20 girls. There is one set of F 2 twins, a boy and a girl.

TABLE VI. MARITAL HISTORY OF F 1 CHILDREN

34	F	1	children have already married (14 males and 20 females)
31	F	1	children have already borne 43 F 2 children
42	F	2	children are living and normal
3	F	1	children are now pregnant
1	F	2	child was born at term, normal, but died after a few breaths; the cause was maternal eclampsia-toxemia

TABLE VII. F 2 GRANDCHILDREN BORN TO IRRADIATED WOMEN

IRRADIATED GRANDMOTHER	DATE TREATED	CHILD (F 1)		DATE BORN	DATE MARRIED	GRANDCHILD (F 2)				
		BOY	GIRL			BOY	GIRL	TWINS	NO.	NOW PREGNANT
C. A.	6/ 9/25		x	1926	1946	1948	1950		2	
E. A.	4/16/29		x	1936	1956		1957		1	
B. B.	5/10/27	x		1934	1956		1957		1	
M. B.	10/19/27		x	1928	1950	1955	1953		2	
H. B.	3/12/25		x	1926	1949	1950				
						1953				
						1956				
		x		1928	1954		1955		4	
F. C.	10/14/27	x		1931	1951	1953			1	
B. C.	10/27/27	x		1928	1954	1956	1955		2	
D. S.	1/10/28		x	1934	1955				0	
S. E.	10/22/24	x		1925	1952	1954	1956		2	
G. G.	2/18/26		x	1934	1953	1955	1957		2	
S. F.	4/13/31		x	1932	1956				0	
A. G.	9/27/29		x	1930	1951	1956	1957		2	
I. G.	9/17/26		x	1927	1951	1955	1957		2	
		x		1930	1954	1956			1	
L. K.	3/18/26	x		1927	1950	1951				
						1955			2	
J. L.	4/ 2/35		x	1936	1953	1956	1955		2	
R. L.	10/ 1/28		x	1930	1952	1955			1	
						1958				x
			x	1934	1956	Divorced			0	
B. M.	1/29/31		x	1932	1955				0	
M. M.	2/22/27	x		1928	1948	1950	1951		2	
			x	1930	1952		1958	1952	3	
			x	1934	1952					x
M. Me.	2/21/27		x	1931	1951	1952	1954			
							1956		3	
L. M.	5/13/29	x		1934	1956		1957		1	
		x		1932	1954				0	
E. R.	10/10/28		x	1929	1951	1952	1955		2	
			x	1936	1957				0	
M. R.	7/31/30	x		1931	1950	1952			1	
L. S.	1/13/25		x	1928	1949	1952	1951		2	
		x		1926	1956		1957		1	
F. S.	11/ 3/26	x		1930	1952					x
		x		1927	1956				0	
N. U.	8/12/27		x	1928	1952	1954			1	
Total									43	3

Table VII shows in detail the data regarding these married F 1 children and their F 2 offspring. All of the living grandchildren have been carefully

examined by competent pediatricians and have been found normal mentally and physically. (One grandchild of G. G. died shortly after birth of delayed delivery associated with maternal eclampsia. Subsequently, however, the mother of this child has given birth to another normal child.)

Conclusion

In view of 32 years of experience in the treatment of married women for infertility and sterility, and the results achieved in the production of healthy children and grandchildren, my current reappraisal would indicate that this therapeutic procedure is justifiable.

This form of therapy has been followed by an over-all incidence of 3.7 per cent of abnormalities (only a small percentage of these are genetic in character) as against a 7 per cent occurrence of abnormalities usually noted in the children of the general population. The F 2 children born to children of irradiated women are normal in every respect, and any adverse criticism based solely on animal experimentation cannot properly be extrapolated for results in human beings.

References

1. Kaplan, Ira I.: Am. J. Obst. & Gynec. **15**: 658, 1928.
2. Kleegman, S.: Personal communication. Wolf, S.: Am. J. Obst. & Gynec. **59**: 259, 1950.
3. Corner, G. W.: Fertil. & Steril. **8**: 494, 1957.
4. McIntosh, R., Merritt, K. K., Richards, M. R., Samuels, M. H., and Bellows, M. T.: Pediatrics **14**: 505, 1954.
5. Jacobziner, H., Pakter, J., Gold, E. M., and Rich, H.: New York J. Med. **57**: 3453, 1957.
6. Davis, M. E., and Potter, E. L.: Pediatrics **19**: 719, 1957.
7. Neel, J. V., and Schull, W. J.: National Academy of Science Publication No. 461, 1956.
8. Kaplan, Ira I.: Am. J. Obst. & Gynec. **23**: 426, 1932.
9. Stewart, A., Webb, J., Giles, D., and Hewitt, D.: Lancet **2**: 447, 1956.
10. De Vore, J. W., and Doan, C. A.: Ann. Int. Med. **47**: 300, 1957.
11. Brues, A. M., and Sacher, G. A.: In Nickson, J. J., editor: Symposium on Radiobiology, New York, 1952, John Wiley & Sons Inc., pp. 441-465.
12. Muller, H. J.: Science **66**: 84, 1927.
13. Russell, W. L.: In Nickson, J. J., editor: Symposium on Radiobiology, New York, 1952, John Wiley & Sons Inc., pp. 427-440.
14. Slatis, H. M.: Personal communication.
15. Neel, J. V.: J. A. M. A. **166**: 908, 1958.
16. Rubin, I. C.: Personal communication.

755 Park Avenue
New York 21, N. Y.

Reviews and Abstracts

EDITED BY LOUIS M. HELLMAN, M.D.

REVIEWS OF NEW BOOKS

Textbook of Gynecology. By John I. Brewer. Second edition. 742 pages with 204 figures. Baltimore, 1958, Williams & Wilkins Company. $15.00.

Gynecology, published in 1950, has been revised by Dr. John Brewer and entitled *Textbook of Gynecology.* The material in the previous edition has been expanded and considerable new material added.

The subject material is presented along the lines of growth and development of the female. The first part, which deals with symptoms and findings, is divided into three sections pertaining to the three major periods of a woman's life: childhood, maturity, and old age. Part two is devoted to the major entities.

A chapter on endocrinology is contributed by Edwin J. DeCosta. This is a good summary stressing clinical application, with a conservative approach to therapy.

The numerous photomicrographs are excellent but the halftones taken at operations to illustrate the pathology found are not as satisfactory. There are adequate references at the end of each chapter and a subject index. The author has succeeded in producing a compact, concise, readable, and well-balanced presentation.

Anomalías morfológicas de la placenta y su significado clínico. By Oscar Agüero. 107 pages, with 27 illustrations. Caracas, 1957, Artegrafia, C. A.

Dr. Agüero collected 10,000 consecutive placentas between March, 1945, and September, 1948, and studied them according to their size, shape, weight, and the presence or absence of any gross abnormalities. At the same time he indexed the maternal history and the course of labor. He discusses the following abnormalities: circumvallate placenta, multiple placentas, bilobed placentas, battledore placentas, cysts of the placenta, aberrent vessels and other vascular anomalies, velamentous insertion of the cord, succenturiate lobes and other rare anomalies, viz., membranous placenta, annular placenta, and fenestrated placenta.

Under each heading, the type of placenta under discussion is defined; the incidence is noted, the clinical significance and, occasionally, the various theories concerning the etiology of the particular anomaly are mentioned. Each type of anomaly is also illustrated by excellent black and white photographs. The over-all incidence of abnormalities was 9.33 per cent, which is higher than that usually seen in the literature. This small monograph represents a tedious and well-executed work.

Drugs, Their Nature, Action and Use. By Harry Beckman. 728 pages with 126 figures. Philadelphia, 1958, W. B. Saunders Company. $15.00.

Dr. Beckman has written a valuable text for students and clinicians alike. In concise fashion, the pharmacology and clinical uses of drugs have been set forth so as to provide a fast and reliable review of the essentials of individual drug action and application. In no way does the author claim to cover all aspects of pharmacology, but he has provided a well-organized, well-indexed volume of drugs used in practice today with references for more detailed information if desired. The chapter on drugs acting on uterine musculature is superior "clinically" to the treatment in most of the standard texts of pharmacology in that the information given is correlated closely with the stages of labor which are described in some detail. The book is written with personal comments by the author which lend an unusual and interesting flavor to the text material.

Hormones in Blood. By G. E. W. Wolstenholme and Elaine C. P. Millar. 416 pages with 74 illustrations. Boston, 1957, Little, Brown & Company. $9.00.

Recordings of the forty-third international conference held under the auspices of the Ciba Foundation in 1950 dealing with separate topics are discussed by eminent authorities in their respective fields. At the conclusion of each presentation there is discussion by other participants and in many instances the latter aspect is the more enlightening.

There are two major themes considered: how hormones are transported in the blood, and how hormone levels in the blood can be measured.

The book is filled with a large amount of valuable information applicable to research problems rather than clinical problems. It would be an adjunct in the laboratory or research library, but offers little for the practicing physician.

Principles of Gynaecology. By T. N. A. Jeffcoate. 696 pages, and 436 figures. London, 1957, Butterworth & Co., Ltd.

Anyone who knows or who has listened to Mr. Jeffcoate will have been impressed by his clarity of thought and lucidity of presentation. These characteristics are abundantly evident in *Principles of Gynaecology*. Combined with some of the finest medical illustrating seen by this reviewer, this text from the very first opening of the cover appeared to be well above average. Just to cite one example: The very difficult subject of embryologic development of the urogenital system is covered in the seventh chapter in 7 pages. The superbly conceived diagrams and concise clear English make even the tyro feel like an embryologist.

Wherever one turns in the book one is impressed that the very essentials of knowledge have been presented without padding of any sort. The chapters on endometriosis, genital cancer, and genital prolapse are particular examples. Unlike so many writers of recent gynecologic texts, Jeffcoate still admits that there are surgical aspects to his specialty and he is quite ready to present at least the basic principles of important procedures.

This text is a distillate of Mr. Jeffcoate's teaching and knowledge of his specialty. Unfortunately, there is almost no reference to source material. This is indeed a pity for it tends to turn pedantic a text which by all other measures stands far to the fore.

BOOKS RECEIVED FOR REVIEW

Abortion in the United States. By Mary Steichen Calderone, with an introduction by M. F. Ashley Montagu. 224 pages, 1 figure, and 38 tables. New York, 1958, Hoeber-Harper, $5.50.

Care of the Premature Infant. By Evelyn C. Lundeen and Ralph H. Kunstadter. 367 pages with 87 illustrations. Philadelphia, 1958, J. B. Lippincott Company. $8.00.

Clinical Enzymology. By Gustav J. Martin. 241 pages, 2 plates, 6 tables, and 5 figures. Boston, 1958, Little, Brown & Company. $6.00.

Family-Centered Maternity Nursing. By Ernestine Wiedenbach. 345 pages, 25 figures, and 11 charts. New York, 1958, G. P. Putnam's Sons. $5.50.

Hermaphroditism, Genital Anomalies and Related Endocrine Disorders. By Howard W. Jones, Jr., and William Wallace Scott. 456 pages, 466 figures, and 12 tables. Baltimore, 1958, Williams & Wilkins Company. $16.00.

Human Infertility. By C. Lee Buxton and Anna L. Southam. 229 pages, 25 tables, and 43 figures. New York, 1958, Hoeber-Harper, $7.50.

Modern Trends in Endocrinology. By Harold Gardiner-Hill. 311 pages, 15 figures, 8 tables, and 1 plate. New York, 1958, Hoeber-Harper. $13.50.

Pediatric Gynecology. By Goodrich C. Schauffler. Fourth edition, 349 pages with 84 illustrations. Chicago, 1958, The Year Book Publishers, Inc. $9.00.

Pregnancy, Birth and Abortion. By Paul H. Gebhard, Wardell B. Pomeroy, Clyde E. Martin, and Cornelia V. Christenson. 282 pages, 17 figures, and 75 tables. New York, 1958, Hoeber-Harper, $6.00.

La Terapia del cancro dell'utero. Riunioni medico-chirurgiche internazionali 1957, atti del simposio sulla terapia del cancro dell'utero, Pres. del simposio Prof. A. Brunschwig. 435 pages, 4 illustrations, 72 figures, and 77 tables. Torino, Italy, 1958, Edizioni Minerva Medica. L.5,000.

Textbook of Obstetrics and Obstetric Nursing. By Mae M. Bookmiller and George Loveridge Bowen. Third edition. 725 pages, 372 figures, and 1 table. Philadelphia, 1958, W. B. Saunders Company.

SELECTED ABSTRACTS

The British Journal of Radiology

Vol. 30, 1957.

Bewley, D. K., Laws, J. W., and Myddleton, C. J.: Maternal and Foetal Radiation Dosage During Obstetric Radiographic Examinations, p. 286.

Clayton, C. G., Farmer, F. T., and Warrick, C. K.: Radiation Doses to the Fetal and Maternal Gonads in Obstetric Radiography During Late Pregnancy, p. 291.

Ardran, G. M., and Crooks, H. E.: Gonad Radiation Dose From Diagnostic Procedures, p. 295.

Because of the current interest in the influence of radiation on this and following generations, Table I from each of these papers, respectively, is reproduced. The data for

the table in the paper by Bewley and associates were obtained from 2 bolus-filled plaster phantoms modeled by a thin, small and an obese, large gravida at term. The results reported by Clayton were obtained from a water phantom, while those of Ardran were estimated for the female, with supporting data obtained from a "Mix D" phantom 9 inches thick.

The radiation to the maternal ovaries obtained by Bewley is markedly lowered from that of Clayton by the reduction of the current (mAs) and increase in voltage; also by the use of high-speed screen and films.

LOUIS M. HELLMAN

TABLE I.* DOSES PER RADIOGRAPH, IN ROENTGENS
(Red Seal Film. 1 mm. Al Filter Added. High Kilovoltage Screens)

	SMALL TERM				LARGE TERM		
	LATERAL	INLET	OUTLET	TOTAL	LATERAL	P.A.	TOTAL
kVp	120	120	108		111	99	
mAs	75	130	75		50	50	
F.F.D.	36 in.	36 in.	40 in.		40 in.	40 in.	
F.S.D.	49 cm.	48 cm.	69 cm.		63 cm.	71 cm.	
Cone area at 30 cm. F.D.	10 × 10 cm.	10 cm. dia.	10 cm. dia.		13.5 cm. dia.	13.5 cm. dia.	
Reference point: Maternal ovary	0.1	0.5	0.03	0.6	1.0	0.2	1.2
Foetal gonads: Vertex presentation							
5 cm. deep	0.06	4.6	0.01	4.7	0.15	0.12	0.27
8 cm. deep	0.14	2.8	0.02	3.0	0.18	0.17	0.35
Breech presentation	0.41	0.04	0.20	0.6	0.13	0.15	0.28
Average	0.1	2.8	0.02	2.9	0.2	0.15	0.35

*Taken from Bewley, Laws, and Myddleton with slight changes.

TABLE I.* MEASURED PRIMARY BEAM DOSES AT POINTS CORRESPONDING TO MATERNAL AND FOETAL GONADS AND THE CENTRE OF THE FOETUS IN A PATIENT OF AVERAGE SIZE IN LATE PREGNANCY FOR EACH OF THE STANDARD RADIOGRAPHIC PROJECTIONS

PROJECTION (F.F.D. = 36 IN.)	kV	mA	EXPOSURE (SECONDS)	DOSE TO THE FOETAL GONADS IN L.O.A. PRESENTATION (r)	DOSE TO THE CENTRE OF THE FOETUS (r)	DOSE TO THE MATERNAL OVARIES (r)
Posteroanterior abdomen (prone)	60	200	0.5	0.03	0.06	0.09 to each
Anteroposterior abdomen (supine)	62	200	0.5	0.32	0.21	0.10 to each
Lateral abdomen	67.5	200	0.6	0.10	0.16	0.45 and 0.02
Lateral pelvis Erect or semierect				Foetal gonads are outside the primary beam in cephalic presentations		
(*a*) Moving grid only	75	200	1.5		0.9	1.75 and 0.05
(*b*) Fixed and moving grid	85	200	1.5		1.15	2.25 and 0.06
Pelvic outlet view	72.5	200	0.8	ditto	0.20	0.21 to each
Thoms' view Oblique anteroposterior "brim view"	80	200	2.0	3.0	1.1	1.4 to each
Chassar-Moir's modification of Thoms' view	80	200	1.0	Foetal gonads are outside the primary beam in cephalic presentations	0.47	0.44 to each

*From Clayton, Farmer, and Warrick with slight changes.

TABLE I.* RADIATION DOSE RECEIVED BY THE SKIN AND GONADS IN RADIOGRAPHIC EXAMINATIONS AT A.E.R.E.

EXAMINATION	kV	mAs	FOCUS-FILM DISTANCE	ADDED FILTRATION	DOSE PER EXPOSURE (WITH BACK SCATTER)		
					SKIN DOSE (mr)	MALE GONAD DOSE (mr)	FEMALE GONAD DOSE (mr)
Sinuses, O.M.	80	40	27 in.	3 mm. Al	1040	0.1	0.05
Hand and wrist, posteroanterior	46	50	27 in.	3 mm. Al	100	0.04	0.01
Chest, posteroanterior	90	3	72 in.	3 mm. Al	8	0.01	0.02
Chest, tomogram (apices), anteroposterior	85	12 B	100 cm.	3 mm. Al	110	0.01	0.02
Dorsal spine, anteroposterior	75	80 B	110 cm.	3 mm. Al	480	1.0	1.3
Lumbar spine, anteroposterior	75	80 B	110 cm.	3 mm. Al	480	0.5†	95.0
Lumbar spine, lateral	85	300 B	110 cm.	3 mm. Al	2000	2.25	270.0
Lumbar sacral joint, lateral	90	400 B	110 cm.	3 mm. Al	3000	2.0	350.0
Pelvis, anteroposterior	75	80 B	110 cm.	3 mm. Al	480	20.0†	80.0
Abdomen, anteroposterior	75	60 B	110 cm.	3 mm. Al	360	0.5†	75.0
Abdomen, barium meal, prone (H.V.)	90	20 B	110 cm.	3 mm. Al	130	1.5	20.0
I.V.P. renal, anteroposterior	75	80 B	110 cm.	3 mm. Al	480	0.5†	95.0
I.V.P. bladder, anteroposterior	75	80 B	110 cm.	3 mm. Al	480	10.0†	80.0
Knee, anteroposterior	82	25 B	110 cm.	3 mm. Al	180	1.25	0.4
Ankle, anteroposterior	70	30 B	36 cm.	1 mm. Al	200	0.1	0.025
Duodenal cap series, posteroanterior (H.V.)	90	15 G	18 in.	5 mm. Al + TT	130	0.05	0.05
Fluoroscopy chest (I.I.)	75	90 G (3 minutes)	18 in.	5 mm. Al + TT	900	3.0	3.0
Fluoroscopy, barium meal (I.I.)	75	150 G (5 minutes)	18 in.	5 mm. Al + TT	1500	5.0	5.0

*From Ardran and Crooks with slight changes.
†Lead rubber protection.
B, Bucky.
G, Stationary grid.
H.V., High voltage screen—Ilford Red Seal film. Other examinations: Par Speed screens and Red Seal film; extremities, Ilfex film.
I.I., Image intensifier. Tube current, 0.5 – 1.0 mA.

Bulletin of the Sloane Hospital for Women

Vol. 4, 1958.

Reisfield, Donald R.: Congenital Defect in the Fetal Membranes: A Condition Simulating Spontaneous Rupture, p. 16.

General management of the patient admitted with apparent rupture of the membranes at the Sloane Hospital is outlined. This therapy consists of immediate bed rest, verification of amniotic fluid leakage with the Nitrazine test or direct visualization of the external cervical os, antibiotics (Achromycin, 250 mg. every 4 hours) if labor does not ensue in 24 hours and, finally, discharge if leakage stops after 24 hours of ambulation.

A case is presented as an illustration of the rather paradoxical situation of a patient found to have true leakage of amniotic fluid and still to require an amniotomy at delivery. After the onset of forceful uterine contractions amniotic fluid flowed heavily. At delivery an amniotomy was performed with a subsequent gush of fluid. Examination of the placenta showed it to be circumvallate and the membranes to contain one jagged tear from the amniotomy and a 3 cm. fenestration with thickened and rolled edges located near the placental margin. It was concluded that there was no leakage of fluid from this defect

previously for it was not until the onset of labor that the intrauterine pressure became great enough to force the fluid between the membranes and the decidua to the outside. The author then discusses other causes of amniotic fluid leakage with gross rupture of the membranes:

1. The so-called "high leak" or rupture of the amniochorion with subsequent reconstitution which may arise secondary to the trauma of attempted abortion, coitus, infection, or infarction of the membranes, or markedly elevated intrauterine pressures.

2. The "double" or "split" sac with the separation of the amnion from the chorion. Fluid passes through the permeable amnion and drains to the outside via minor tears in the more friable chorion.

LAURENCE SONDERS

The Canadian Medical Association Journal

Vol. 78, 1958.

Swyer, Paul R., and Weight, John: The Control of Supplemental Oxygen by Oximetry, p. 231.

This paper describes experience in the control of supplemental oxygen with the use of the diamagnetic oxygen analyzer and the Wood spectrophotometric ear oximeter in the assessment of arterial oxygen saturation.

The 31 patients investigated were receiving supplemental oxygen on the clinical grounds of cyanosis of central origin or dyspnea or both. In 14 patients receiving supplemental oxygen on clinical grounds, the arterial oxygen saturation was above 95 per cent when they were removed from oxygen and tested in air. They were probably receiving oxygen unnecessarily.

In 14 cases there was less than 95 per cent saturation at the first examination. A significant proportion of these patients required more than 40 per cent oxygen initially to achieve an approximately normal arterial oxygen saturation. The tendency was for the need for supplemental oxygen to drop progressively with the passage of time. No surviving infant required supplemental oxygen for longer than 5 days.

It was felt that if an infant's blood can be shown to be 95 to 98 per cent saturated oximetrically, the arterial oxygen tension is not likely to be at dangerous levels. With approximately 96 per cent arterial saturation measured by ear oximeter, the partial pressure of oxygen in arterial blood will remain close to the safe 100 mm. Hg level.

Oximetry can be used to control administration of supplemental oxygen at the minimum level necessary to secure oxygenation of arterial blood and avoid hyperoxia in infants in the weight groups susceptible to retrolental fibroplasia, and hypoxia due to adherence to a rigid rule-of-thumb limitation of supplemental oxygen.

JOHN J. DETTLING

Douglas, R. G., Buchman, M. L., and MacDonald, F. A.: Recent Trends in Hysterectomy in Gynecological and Obstetrical Practice, p. 1065.

Recent trends in hysterectomy were discussed as they occurred at the New York Lying-In Hospital between the years 1950 and 1956, when 3,233 hysterectomies were performed. Of the operations performed, 74.9 per cent were total abdominal in type; 3.7 per cent were subtotal; 18.2 per cent were vaginal; and 3.2 per cent were radical procedures. After 1946, there was a rapid reversal from subtotal to total hysterectomy. The incidence of vaginal hysterectomy has almost doubled since 1950.

The median age of the patients who had abdominal hysterectomies was 45.3 years, whereas for those who had vaginal hysterectomies it was 54.6 years. The anesthesia of choice was general anesthesia with thiopentone induction, followed by nitrous oxide-oxygen-ether or cyclopropane.

Myomas were the most frequent indication for the abdominal operation, and prolapse of the uterus for the vaginal procedure. The technique employed in total abdominal

hysterectomy is a modification of either the Richardson or the Aldridge method, except when adenocarcinoma is present. A variation of either the Heaney or Bissell-Goffe technique is used for vaginal hysterectomies.

Postoperative complications were recorded in 49.6 per cent of the patients. One out of 5 patients developed urinary tract complications and next, amounting to 16.3 per cent, were temperature elevations of undetermined etiology. Antibiotics were employed in 74 per cent of the patients for prophylactic or therapeutic reasons. Cardiovascular complications included anemia, thrombophlebitis, hemorrhage, and hematoma.

The pathological reports following hysterectomy disclosed that 64 per cent of the uteri contained myomas; 16.6 per cent contained endometrial polyps; 20.4 per cent exhibited atrophic endometrium; 6.2 per cent contained a malignant tumor of the cervix. The importance of routine cytological smears or a diagnostic dilatation and curettage prior to hysterectomy was stressed.

The gross mortality rate was 0.3 per cent and the corrected rate was 0.15 per cent.

JOHN J. DETTLING

Cancer Research

Vol. 18, 1958.

Donnelly, A. J., Havas, H. F., and Groesbeck, M. E.: Mixed Bacterial Toxins in the Treatment of Tumors. I. Methods of Preparation and Effects on Normal and Sarcoma 37-bearing Mice, p. 141.

Normal and sarcoma 37-bearing mice were treated with varying strains of Streptococcus and *Serratia marcescens,* and combinations of strains of the two. Some cultures were grown separately and mixed before heat sterilization; in other preparations, the Serratia were inoculated into the growing Streptococcus culture at a specified time, depending on the type of preparation.

Ascitic fluid containing sarcoma 37 was inoculated subcutaneously into mice, and after 7 days those with tumors of specific size were used in the experiment.

Survival time, tumor size, and percentages of complete regressions were all considered as indices of efficacy. The final criterion of the effectiveness of the toxins, however, was the complete regression of the tumor at the completion of the experiment, and not simply a reduction in size of the tumor.

Over 100 preparations comprising different strains of bacteria and modes of growth were tested. Each batch of toxins was tested in at least 32 mice. It was found that the mode of growth, as well as the bacterial strain, plays a determinant role in the ensuing oncolytic potency. From the regression rates it was found that some of the mixed preparations were less toxic than, and superior in oncolytic activity to, those from *Serratia marcescens* alone or its purified polysaccharide.

Possible mechanisms responsible for tumor destruction discussed are:

1. The gram-positive exotoxins from Streptococcus are mostly proteins which resemble enzymes. They might catalyze production of active hydrolytic enzymes from inactive precursors in the body or split off an active component from a less active precursor of the gram-negative Serratia. Synergistic effects can thus be produced which neither organism would achieve alone.

2. Tumor destruction might also be brought about by a modified Shwartzman reaction prepared and elicited by antigenically similar constituents of the tumor and bacterial cell.

RICHARD J. CALAME

Donnelly, A. J., Havas, H. F., and Groesbeck, M. E.: Mixed Bacterial Toxins in the Treatment of Tumors. II. Gross and Miscropic Changes Produced in Sarcoma 37 and in Mouse Tissue, p. 149.

The mixed bacterial toxins *(Streptococcus pyogenes and Serratia marcescens),* when given to normal mice at relatively high dosages, produce a nonspecific alarm reaction.

The changes in the lymphoid tissues are morphologically similar to those produced by an effective antigen. Trapping of leukocytes occurs in pulmonary alveolar walls.

In mice bearing sarcoma 37, the same general changes are produced with much smaller doses of mixed toxins; the tumors undergo degeneration, and more than half are completely destroyed. The hemorrhage and necrosis occurring in the treated tumors are characterized histologically by clouding, cellular degeneration, and edema, followed by cell shrinkage, nuclear pyknosis, and disintegration, with eventual absorption of the cellular debris. Healing and scar formation follow. Possible mechanisms involving the tumor-necrotizing action of bacterial products are considered.

RICHARD J. CALAME

Deutsche medizinische Wochenschrift

Vol. 50, 1957.

Mirat, B., and Wand, H.: The Causes of Stillbirth, p. 2065.

Since the inauguration of death certificates in the province of Hessen, the data reported regarding fetal death and stillbirth in the years 1955-1956 have been analyzed. For this purpose the World Health Organization's classification was employed.

The fetal mortality was found to be the highest in the first postnatal week and seems to be resistant to any measure of improvement in this period. The most common among the specified causes of death were anomaly of the umbilical cord and placenta (16.5 per cent) with greater frequency of the former; then, congenital malformation of the newborn (9 per cent), dystocia (8.4 per cent), and prematurity (8.3 per cent). The incidence of postmaturity as a cause was 2.1 per cent. Four and nine-tenths per cent of the deaths were stillbirths due to disease and pathological distress of the mother during pregnancy and labor. As etiological factors, diabetes mellitus and syphilis were surprisingly low.

C. BERENKEY

Journal of Pediatrics

Vol. 50, 1957.

Parkinson, R. P.: A Study of Venous Pressure in the Newborn Infant, p. 174.

A method of recording venous pressures in the newborn infant is presented. Seventeen determinations were recorded through the umbilical vein. Sixteen determinations were obtained between 60 seconds and 240 seconds following clamping of the cord. The mean venous pressure was 85 mm. of water with a range of 80 to 180. The Burch-Winsor phlebomanometer was the instrument used for the determinations. It was noted that stripping of the cord was associated with markedly increased recordings.

SCHUYLER G. KOHL

Graham, F. K., Pennoyer, M. M., Caldwell, B. M., Greenman, M., and Hartman, A. F.: Behavior Test Performance of Newborns with Anoxia, p. 177.

A battery of five behavioral tests designed and standardized for newborn infants was administered to a group of 60 "anoxic" infants, and to a group of 62 normal infants. The tests were the following: pain threshold test, maturation scale, vision scale, irritability rating, and muscle tension rating. Impairment in test performances reflected the seriousness of the clinical condition. It might be worth while to prove the observations by performing the tests on a random sample of all newborn infants without prior knowledge of the presence or absence of "anoxia." Similar work has been performed in France by Thomas and it is presently under investigation in other centers.

SCHUYLER G. KOHL

Proceedings of the Society for Experimental Biology and Medicine

Vol. 97, 1958.

Davis, E. V., Glover, F., and McLimans, W. F.: Proliferation of Human Amnion Cells (FL Strain) in Submerged Culture, p. 454.

Cells isolated from human amnion are useful for the isolation of certain viruses and, in order to obtain a uniform supply from a single cell line, tissue culture was used. The culture medium was made up of 10 per cent horse serum (inactivated at 56° C. for 30 minutes) and 90 per cent modified Eagle's medium. In the modification, glutamine, leucine, isoleucine, arginine, and methionine were added at concentrations 2 to 10 times those normally used in Eagle's medium.

The cell multiplication rate approached a logarithmic growth curve with generation times of 25 to 36 hours. The cultures were easily maintained for periods up to 1 to 2 months and more than 98 per cent of the cells were viable as judged from trypan blue staining. The cells retained their susceptibility to type 4 adenovirus.

LEON C. CHESLEY

Proceedings of the Staff Meeting of the Mayo Clinic

Vol. 32, 1957.

Berkson, J., Harrington, S. W., Clagett, O. T., Kirklin, J. W., Dockerty, M. B., and McDonald, J. R.: Mortality and Survival in Surgically Treated Cancer of the Breast: A Statistical Summary of Some Experience of the Mayo Clinic, p. 645.

The article consisted of two parts. Part I was concerned with "The Relation of Survival to Various Biometric Factors." Part II was concerned with "The Comparison of Radical Mastectomy (Mayo Clinic) With Simple Mastectomy and Radiotherapy (McWhirter From Edinburgh)." The policy initiated in Edinburgh in 1941 consisted of a sharp break with the classic Halsted procedure of radical mastectomy with excision of axillary lymph nodes. The policy was in favor of simple mastectomy followed by a full course of radiotherapy for a period of 3 or 4 weeks.

In the Edinburgh experience, under the policy of simple mastectomy with radiotherapy, the 5 year survival rate of patients with cancer of the breast occurring in association with pregnancy or lactation was 35 per cent. Regarding these results McWhirter says, "Prior to 1941 none of the patients with carcinomata occurring in association with pregnancy or lactation survived for five years."

The experience at the Mayo Clinic shows that the 5 year survival rate for treatment by radical mastectomy prior to 1941 was 17.6 per cent. After 1940, the rate with radical mastectomy was 58.5 per cent.

On the basis of the experience of the Mayo Clinic, as shown in the 5 year survival rate, the results of treatment of carcinoma of the breast with radical mastectomy are superior to those with simple mastectomy followed with radiotherapy.

JOHN J. DETTLING

Wiener medizinische Wochenschrift

Vol. 107, September 7, 1957.

Spielman, W.: Difficulties in the Diagnosis of Extrauterine Pregnancy, p. 727.

The author points out that scarcely 10 per cent of patients with extrauterine pregnancy present the typical textbook picture. The principal cause of death in extrauterine pregnancy seems to be failure to make the diagnosis; other causes of death are undue delay in operation and insufficient blood replacement. Although the last two factors have

become less important recently because of the development of blood banks and increased transportation facilities, mistakes in diagnosis remain the responsibility of the attending physician. The author stresses the importance of evaluation of pain, and the essential contribution of an accurate history. He points out that cul-de-sac puncture, which has been reported as making the diagnosis in 90 per cent of cases, must be done only with the patient in the hospital and with preparations for immediate operation already made. The relative value of various laboratory procedures is discussed. The total mortality of tubal pregnancy in Austria is about 2 per cent, but the author implies that this could be reduced in the present state of knowledge to the vicinity of 1 per cent. He points out that in recent series several authors have reported sizable numbers of cases without any deaths, and that laboratory investigations are of only ancillary value in the diagnosis, so that a high index of suspicion in the clinical evaluation of the patient remains of paramount importance.

DOUGLAS M. HAYNES

Vol. 107, October 5, 1957.

Käser, O.: The Influence of Social Factors on Perinatal Mortality, p. 827.

In order to evaluate the influence of social factors on perinatal mortality, the author divided his patients for the years 1950 through 1953 into five groups as follows: private patients, professors' wives, laborers' wives, farmers' wives, and a final miscellaneous group. The author points out that this classification includes the principal categories into which the patients at the University clinic at St. Gall, Switzerland, fall. The social factors studied included general working and living conditions, hygienic surroundings, the quality of the diet, and the varying quality of medical care available to the different social groups during their pregnancies. The total perinatal mortality of the entire group was 4.09 per cent. There was a statistically significant difference between the groups, the private patients showing the lowest perinatal mortality. The frequency of abortion and premature labor was also smaller in the private and academic groups than in the other three. Birth weights were significantly higher in the private patient group than in the remainder. Evaluated by the diastolic blood pressure as a measuring stick, toxemia of pregnancy was seen significantly less often in the private and academic groups than in the other three. A similar but less marked difference was also found for the incidence of proteinuria. The author believes that his investigations indicate that social factors exert significant influence on infant mortality in Switzerland, and may in some complex way be related to the incidence of toxemia, abortion, and premature labor.

DOUGLAS M. HAYNES

Correspondence

Statistical Validity of Figures on Ovarian Carcinoma Therapy

To the Editors:

A great disservice is often done by publishing articles which are statistically invalid, yet intimate the contrary. Such is the case with "A Critical Assessment of the Value of X-ray Therapy in Primary Ovarian Carcinoma" by J. P. A. Latour and B. A. Davis which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNECOLOGY in November, 1957.

In their series of 202 cases of primary ovarian carcinoma treated between 1930 and 1950, 58 of 146 patients treated by surgery alone, or 39.6 per cent, survived 5 years. Of the 56 patients treated by surgery and postoperative irradiation only 17 patients, or 30.2 per cent, survived 5 years. The point which was not stressed was that 41 of the surgically treated cases were Stage 0 or Stage I and only 5 of the patients treated with surgery and irradiation were similarly staged.

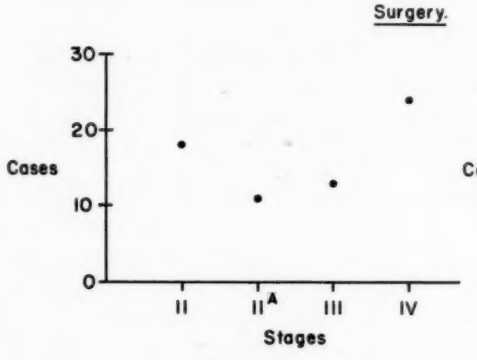

Fig. 1.

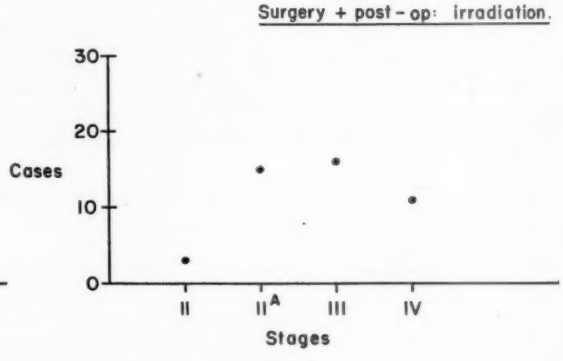

Fig. 2.

Only by carefully controlled series can valid statistical conclusions be obtained. Selection of cases is of utmost importance in survival rates. Certainly in the case of ovarian carcinoma one would not condemn withholding postoperative irradiation in Stage 0 or Stage I cases (yet the weighting of the surgical series with these favorable cases should be stressed in the analysis of over-all survival figures). Of the Stage II through Stage IV lesions in this series of primary ovarian carcinomas the assessment of postoperative irradiation was invalid since selection of cases was not random. This is obvious from Figs. 1 and 2.

In the conclusion the authors state that "It is unfortunate that the literature has spawned an opinion which cannot stand the test of statistical evaluation." With this I

heartily agree; it is even more unfortunate that these same doctors themselves find it necessary to dispense statistically invalid conclusions.

WILLIAM CALDWELL, M.D.

SAN FRANCISCO HOSPITAL
SAN FRANCISCO, CALIF.
MARCH 27, 1958

Reply by Dr. Latour

To the Editors:

We appreciate Dr. Caldwell's criticism of our paper, "A Critical Assessment of the Value of X-ray Therapy in Primary Ovarian Carcinoma," which appeared in the AMERICAN JOURNAL OF OBSTETRICS AND GYNAECOLOGY in November, 1957.

The statistical validity of our material is tenuous, but it is not inferior in this respect to that of any article on this subject so far published. An ideal large series with controls has not yet been reported on this subject which would satisfy a classical statistician.

In spite of defects from the statistical viewpoint, we feel that any one who soberly studies our results cannot fail to come to the same conclusion as we did:

"It is our belief that the value of x-ray therapy as a therapeutic aid in primary carcinoma of the ovary should be critically questioned. This form of treatment is not without its dangers. To retain it one should be able to demonstrate its utility on a sound statistical basis. An assessment of the literature fails to allow such a conclusion. Our own results almost emphatically deny its positive value."

J. P. A. LATOUR, M.D.

ROYAL VICTORIA HOSPITAL
MONTREAL 2, CANADA
MAY 8, 1958

Excision Biopsy of the Cervix

To the Editors:

I have read with great interest Dr. Corbit's article, "Excision Biopsy of the Cervix," in your issue of April, 1958. This interested me, first, because I strongly believe in conization and plastic repair in all cases of chronic inflammation of the cervix. In addition to removing the focus of infection and relieving symptoms, this procedure is undoubtedly of value in diminishing the incidence of cancer by removing the squamocolumnar junction at the external os. Second, I was interested because the method of suturing happens to be exactly the same as I have been using for many years. I first published my modification of the Sturmdorf operation and described the "circular stitch" in *Ginekologja polska* in 1935 and since then have changed some details several times. Later, in 1942, while at Edinburgh University, as acting professor of gynecology in the Polish School of Medicine, I introduced this same suture which Dr. Corbit describes, and have continued to use it up to now with most satisfactory results. For reconstruction of the cervix after conization this technique gives the best anatomical and physiological results, and I have always taught this technique to my assistants and doctors in training.

According to the drawings in Dr. Corbit's article, his way of inserting the suture is identical with mine in every detail, but in my method the cervical canal is wide open during insertion of the suture as I usually perform curettage of the uterus just before conization in these cases.

I excise one half to two thirds of the length of the cervical canal in most cases, as this removes the endocervix well beyond the area characteristically involved. I have found that the cervix does not have to be "nonfunctional" to be suited to this treatment. I have used it in a large number of women in the childbearing age and subsequent labors in these cases

have not been affected unfavorably. It has an advantage over deep cauterization treatment where the large space has to be filled in by granulation tissue, with consequent formation of a thick layer of scar tissue, which often delays or hinders the dilatation of the cervix during labor.

C. Uhma, M.D.

36 Richardson Avenue
Sydney, Nova Scotia
May 5, 1958

Hydatid Degeneration of the Placenta

To the Editors:

In connection with Dr. H. E. Bowles' report (Am. J. Obst. & Gynec. 75: 696, 1958) of a case of hydatid degeneration of the placenta with a live baby, I would like to report a delivery with 85 per cent hydatid degeneration of the placenta which occurred 30 years ago. The birth weight was 4 pounds, 12 ounces, and the placenta was approximately four times the expected size. This baby now has three children, aged 9, 7, and 4, and at birth all had normal placentas.

The mother was 22 years old with a history of four spontaneous abortions before the birth of this baby, and a normal birth 2 years following the birth of the baby.

Harry Kirschbaum, M.D.

19255 Canterbury Road
Detroit 21, Michigan
April 29, 1958

ITEMS

American Board of Obstetrics and Gynecology, Inc.

Applications for certification (American Board of Obstetrics and Gynecology), new and reopened, Part I, and requests for re-examination Part II, are now being accepted. Deadline date for receipt of all such applications is Sept. 1, 1958. No applications can be accepted after that time.

The members of the American Board of Obstetrics and Gynecology wish to announce that at the recent final examinations for certification, a total of 280 were certified out of a group of 383 candidates examined.

It is expected that the new Bulletin of the American Board of Obstetrics and Gynecology will be available some time during the month of July. A copy of the booklet may be obtained by writing to the office of the Secretary.

Robert L. Faulkner, M.D., Secretary
2105 Adelbert Road
Cleveland 6, Ohio

Congress of the Federation of Gynecology and Obstetrics

The Eighteenth Congress of the Federation of Gynecology and Obstetrics in the French Language, organized by the Society of Gynecology and Obstetrics of Paris, will be held in Paris on June 15, 16, and 17, 1959. Presiding will be Professor Lantuejoul.

For further information, write to Dr. Robey, Secrétaire Genéral, 4, Avenue St. Honoré d'Eylau, Paris XVIe.